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S,S'-DIETHYL DITHIOMALONATE AS ETHANOL CARBANION EQUIVALENT IN ANNELATION REACTIONS AND FACIAL SELECTIVITY IN DIELS-ALDER REACTION OF 4,4-DISUBSTITUTED 2,5-CYCLOHEXADIENONES

by

YONGXIN HAN

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

Edmonton, Alberta
Spring, 1992

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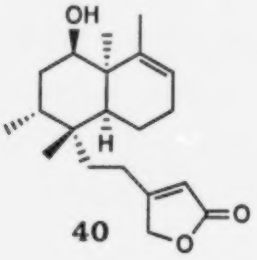
Dedicated to my son, Kevin

ABSTRACT

The first chapter of this thesis describes the annelation reactions involving *S,S'*-diethyl dithiomalonate. It has been shown that *S,S'*-diethyl dithiomalonate undergoes concomitant alkylation reaction and Michael addition with ω-iodo-α,β-unsaturated ketones to give bridged and fused bicyclic carbocycles. The dithiomalonate moiety present in the cyclization products can be easily reduced by W-2 Ra-Ni to the ethanol level.

Studies towards the synthesis of *cis*-clerodanes such as solidagolactone IV (**40**) resulted in an extensive investigation of the facial selectivity in Diels-Alder cycloadditions of 4,4-disubstituted 2,5-cyclohexadienones of general structure **39**. Results are described in the second chapter of this thesis. It was observed that the addition of dienes to dienophiles **114** and **123** occurred in all cases virtually exclusively from the C_4 ester face, resulting in the corresponding adducts such as **118** and **125**. It was further observed that the replacement of the C_4 ethyl ester group in **114** with a *t*-butyl ester group did not change the facial selectivity significantly. However, the reaction of the spiro dienone lactone **142** with 1,3-butadiene showed little facial selectivity. These results are best explained by electronic effects. The reaction of dienes with dienophiles **108**, **163**, **164** and **182** on the other hand occurred preferentially from the C_4 methyl face in each case as expected from steric ground, giving adducts such as **109**, **168**, **174** and **183** as the major products. Adduct **183** served as an intermediate in the projected synthesis of solidagolactone IV.

when **183** was sequentially treated with Me_2CuLi and $LiAlH_4$, keto alcohol **192** was formed. Mesylation of **192** with mesyl chloride and triethylamine afforded mesylate **193**. Reduction of **193** furnished ketone **194** which could in principle be further transformed to naturally occurring *cis*-clerodanes.



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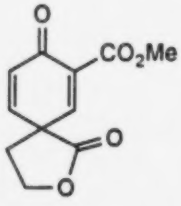
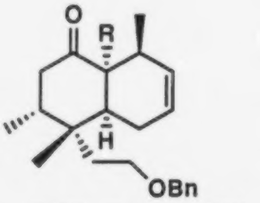
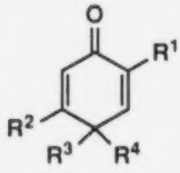


142

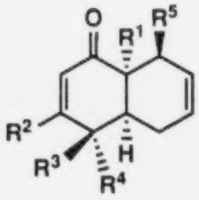


192. R=CH_2OH
193. R=CH_2OMs
194. R=Me



39

108. R^1=CO_2Me, R^2=R^3=Me, R^4=CH_2CH_2OBn
114. R^1=CHO, R^2=H, R^3=CO_2Et, R^4=Me
123. R^1=R^3=CO_2Me, R^2=H, R^4=Me
163. R^1=CHO, R^2=H, R^3=Me, R^4=CH_2CO_2Et
164. R^1=CHO, R^2=H, R^3=Me, R^4=$CH_2CH_2CO_2Et$
182. R^1=CO_2Me, R^2=H, R^3=Me, R^4=CH_2CH_2OBn



109. R^1=CO_2Me, R^2=R^3=R^5=Me, R^4=CH_2CH_2OBn
118. R^1=CHO, R^2=R^5=H, R^3=CO_2Et, R^4=Me
125. R^1=R^3=CO_2Me, R^2=R^5=H, R^4=Me
168. R^1=CHO, R^2=R^5=H, R^3=Me, R^4=CH_2CO_2Et
174. R^1=CHO, R^2=R^5=H, R^3=Me, R^4=$CH_2CH_2CO_2Et$
183. R^1=CO_2Me, R^2=H, R^3=R^5=Me, R^4=CH_2CH_2OBn

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LIST OF ABBREVIATIONS

Ac	acetyl
APT	Attached Proton Test
Ar	Aryl
Bn	benzyl
br	broad
Bu	butyl
cims	chemical ionization mass spectrum
CoA	Coenzyme A
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
DNB	dinitrobenzene
eq	equivalent(s)
Eq.	Equation
Et	ethyl
h	hour
HMPA	hexamethylphosphoramide
hrms	high resolution mass spectrum
i	iso
ir	infrared
LDA	lithium diisopropylamide
m	multiplet

Me	methyl
min	minutes
m.p.	melting point
Ms	methanesulfonyl
nmr	nuclear magnetic resonance
NOE	Nuclear Overhauser Enhancement
p	*para*
PCC	pyridinium chlorochromate
Ph	phenyl
Pr	propyl
Pyr.	pyridine
q	quartet
r. t.	room temperature
t	tert
t	triplet
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	toluenesulfonyl

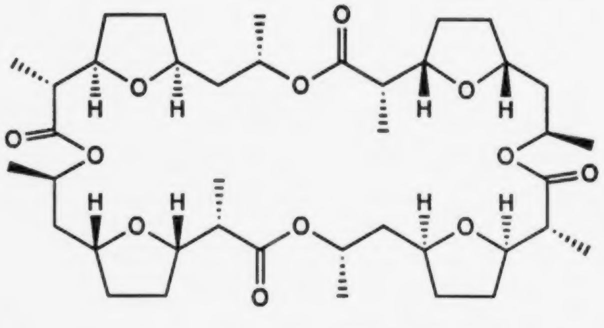
CHAPTER I

S,S'-DIETHYL DITHIOMALONATE AS ETHANOL CARBANION EQUIVALENT IN ANNELATION REACTIONS

Introduction

In 1875, Muhler[1] reported the first preparation of a thiolester, *S*-ethyl acetate, by the reaction of acetyl chloride and ethyl mercaptan. In the following six decades several other preparative methods were reported.[2] However, very limited attention was drawn to the reactivity and synthetic utility of thiolesters until the 1960's,[3] when the role of acetyl-CoA as the important acyl transfer agent in living organisms was recognized.[4] Since then the interest in thiolesters has grown significantly as a result of their widespread applications as useful intermediates in organic synthesis.

The intensive applications of thiolesters have led to the development of many successful preparative methods.[5] In general, carboxylic acids,[6] and their derivatives such as halides,[7] anhydrides[8] and esters[9,10] have been most commonly used as starting materials, along with mercaptans, metal thiolates,[11,12] thioethers,[13,14] phenyl isothiocyanate[15] and methylene sulfide[16] as the thiol moiety. Activating agents such as 1,3-dicyclohexylcarbodiimide (DCC)[17,18] and various phosphorus containing compounds[19-25] have to be used for carboxylic acids and esters.



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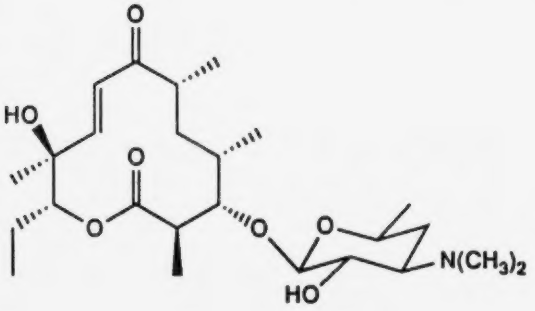

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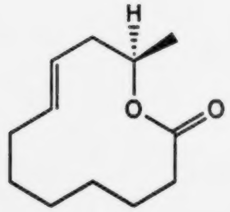

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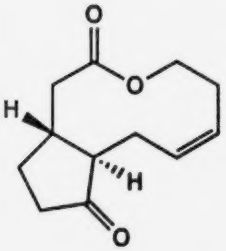

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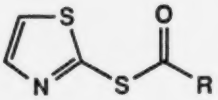
Thiolesters have been used extensively in natural products synthesis in recent years. It is now well established that the thiolester group plays an important role as an activating group in the formation of medium and large size macrolide lactone rings[26-31] which has been a problem in this field for many years. Successful applications have led to the syntheses of many biologically important macrolide lactones such as nonactin (**1**),[32] methymycin (**2**),[33] recifeiolide (**3**)[34] and jasmine ketolactone (**4**).[35]

Unlike ordinary esters, thiolesters can be reduced by sodium borohydride to alcohols. This phenomenon was first observed by Fijita and coworkers[36] on highly activated thiolesters such as **5**. It was reported later by Liu and coworkers[37,38] that ordinary thiolesters could also be reduced. Furthermore, they demonstrated that a thiolester group could be selectively reduced in the presence of other acid derivatives such as amide, ester and nitrile.



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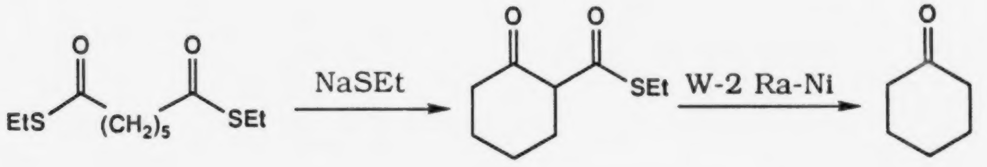
One interesting feature of the thiolester group is its susceptibility to simultaneous desulfurization and reduction upon treatment with Raney nickel (Ra-Ni). It was found that a thiolester could be reduced either to a primary alcohol[39,40] or selectively to the aldehyde stage,[41] depending upon the reactivity of the Ra-Ni used.[42,43]

In a study of the Dieckmann condensation of ω-dithiolesters, Liu and Lai[44] observed that β-keto thiolesters underwent facile dealkylthiocarbonylation reactions when treated with Ra-Ni. For example, treatment of keto thiolester **6** with excess W-2 Ra-Ni resulted in the exclusive formation of cyclohexanone (Scheme 1). Based on these observations, it was suggested[45] that treatment of a 1,3-dithiolester with Ra-Ni should in principle result in the removal of one thiolester moiety with concomitant reduction of the other to the aldehyde or alcohol level. This expectation was substantiated experimentally using a variety of *S,S'*-diethyl dithiomalonate (**7**) derivatives which were readily prepared by alkylation or Michael addition of the parent molecule.



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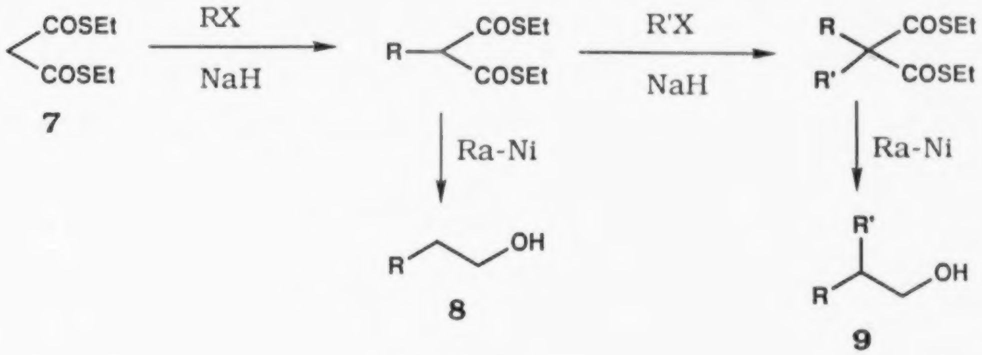
Scheme 1

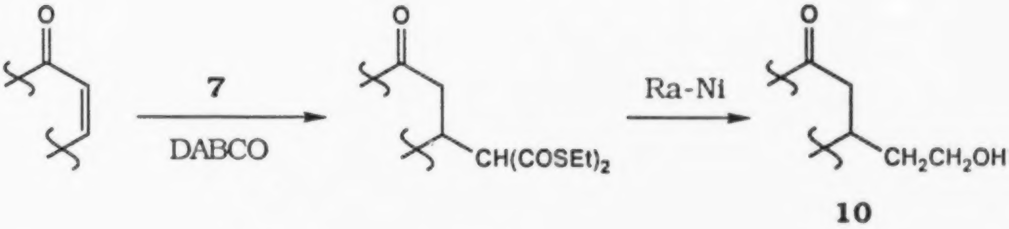
S,S'-diethyl dithiomalonate (**7**) was first prepared by Purvis and coworkers,[46] by the reaction of sodium ethylmercaptide with malonyl chloride. The same compound was later prepared by Scheithauer and Mayer[47] in two steps by reacting malononitrile with ethyl mercaptan and hydrogen chloride followed by hydrolysis. A number of *S,S'*-dialkyl or diaryl dithiomalonates were prepared by Imamoto and coworkers[48] from malonic acid and corresponding thiols in excellent yields using ethyl polyphosphate (PPE) as an activating agent. A simple method was developed by Liu and Lai[45] by reacting malonyl dichloride with ethanethiol. A subsequent modification of this procedure by Liu and Oppong[49] shortened the reaction time from 16 h to 30 min and allowed quantitative formation of **7.**

The chemistry of *S,S'*-diethyl dithiomalonate (**7**) was first briefly explored by Scheithauer and Mayer[47] in 1967. Its reaction with ethyl acrylate and acrylonitrile in methanol using sodium methoxide as a base afforded poor yields of the 1,4-adducts. In addition both mono- and bis-adducts were formed indiscriminately in approximately equal amounts.

In 1979, Liu and Lai[45] succeeded in alkylating **7** with a variety of alkyl halides, using sodium hydride in 1,2-dimethoxyethane (DME). They also demonstrated that upon reacting the resulting dithiomalonate derivatives with Ra-Ni, primary alcohols such as **8** and **9** were obtained in excellent yields (Scheme 2). In 1982, Liu and Oppong[50] reported the Michael addition of dithiomalonate (**7**) with α,β-unsaturated carbonyl compounds of structural diversity. Interestingly, reduction of the Michael adducts with Ra-Ni gave primary alcohols of general structure **10** in high yields, leaving the ketone and other functional groups untouched (Scheme 3). Therefore, the overall transformations illustrated in Schemes 2 and 3 can be considered as the replacement of one or two β-protons of ethyl alcohol by electrophiles or Michael acceptors, using *S,S'*-diethyl dithiomalonate (**7**) as a latent ethanol carbanion equivalent.

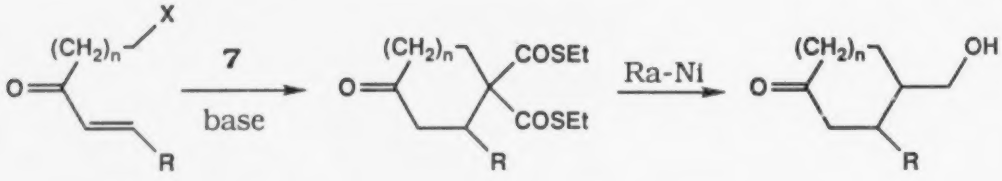

COSEt
COSEt
7
RX
NaH
R
COSEt
COSEt
R'X
NaH
R
R'
COSEt
COSEt
Ra-Ni
Ra-Ni
R
OH
8
R'
R
OH
9

Scheme 2


O
7
DABCO
O
CH(COSEt)₂
Ra-Ni
O
CH₂CH₂OH
10

Scheme 3

An extrapolation of these results suggested an interesting and potentially useful application of dithiomalonate **7** as a convenient source of ethanol carbanion to facilitate the synthesis of functionalized cyclic compounds. As shown schematically in Scheme 4, using a combination of alkylation and Michael reactions, **7** could serve as a masked ethanol carbanion in annelation reactions with an α,β-unsaturated ketone **11** possessing a suitable leaving group. This new annelation process has now been realized experimentally and the results constitute the first part of this thesis.


X
(CH2)n
O
R
7
base
(CH2)n
COSEt
COSEt
O
R
Ra-Ni
(CH2)n
OH
O
R

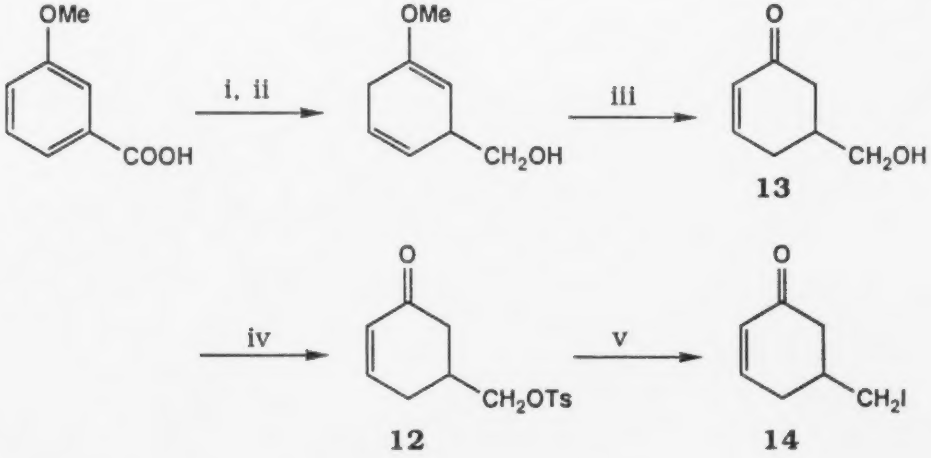
11

Scheme 4

Results and discussion

A. Annelation

S,*S*'-Diethyl dithiomalonate (**7**) used in the studies was prepared according to the procedure described by Liu and Oppong.[49] Thus the reaction of malonyl dichloride with ethanethiol in ether in the presence of pyridine gave a quantitative yield of **7**. To investigate the feasibility of the proposed annelation process, several α,β-unsaturated ketones, each possessing a suitable leaving group, were used. Enone **12** was a known compound in the literature.[51] However, in the present studies, this compound was prepared in a different manner as illustrated in Scheme 5.



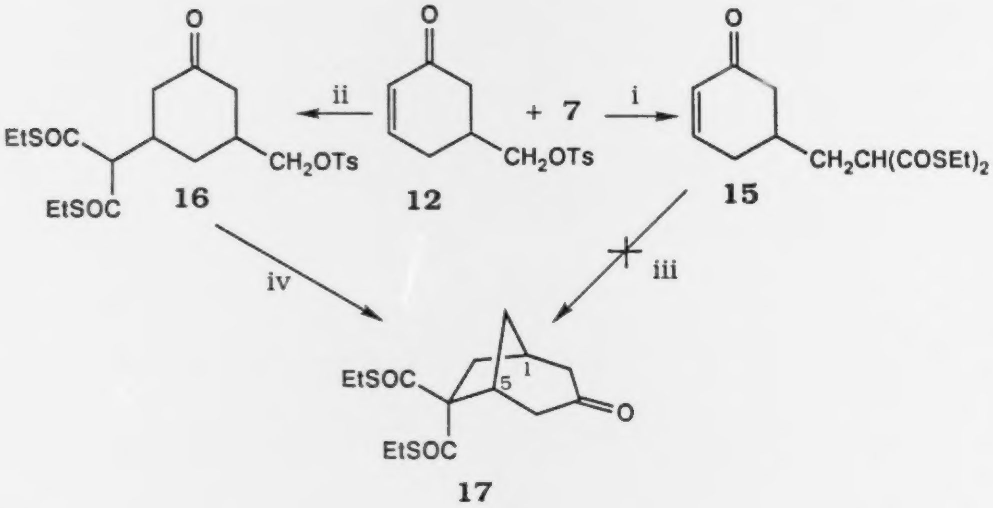
Scheme 5. i, Na-NH_3(l), MeOH; ii, $LiAlH_4$, THF; iii, 1 N HCl, THF, reflux; iv, TsCl, Pyridine; v, NaI, acetone, reflux.

Birch reduction of 3-methoxybenzoic acid[52,53] with sodium in liquid ammonia and methanol followed by lithium aluminum hydride reduction and treatment of the resulting alcohol with aqueous hydrochloric acid furnished the enone alcohol **13** in 60% overall yield. Tosylation of **13** with tosyl chloride and pyridine using a catalytic amount of 4-dimethylaminopyridine (DMAP) in dichloromethane afforded **12** in 70% yield (m.p. 74-75°C; lit.[51] m.p. 74.5-75.5°C). Subsequent substitution reaction of **12** with sodium iodide under Finkelstein reaction conditions[54] gave iodo enone **14** in quantitative yield. The ir spectrum displayed a carbonyl absorption at 1679 cm^{-1} for the ketone carbonyl. In the ^1H nmr spectrum, the vinylic protons appeared at δ 6.97 (ddd, J = 10, 6, 2 Hz, β-H) and 6.00 (dm, J = 10, α-H). The two methylene protons adjacent to the iodo group appeared at δ 3.25 as a multiplet. In the mass spectrum, the molecular ion peak appeared at m/z 235.9709, in agreement with the formula C_7H_9OI.

In early experiments, cyclohexenone **12** was treated with dithiomalonate **7** in DME in the presence of sodium hydride or 1,4-diazabicyclo[2.2.2]octane (DABCO) which were successfully used previously to effect alkylation[45] and Michael addition,[50] respectively. Neither of these bases were found to be effective for the desired cyclization. With sodium hydride, only the substitution product **15** was obtained in 40% yield along with extensive decomposition. The ir spectrum of **15** displayed a broad absorption band at 1666-1690 cm^{-1}. That the α,β-unsaturated ketone unit was retained was indicated by the signals at δ 7.10 (dm, *J* = 10 Hz, β-H) and 6.10 (br d, *J* = 10, α-H) in the ^{1}H nmr spectrum. The signals for the tosyl moiety in the starting material disappeared. The multiplets at δ 3.30 was attributed to the the methine proton of the thiomalonate moiety, and the signals at δ 2.95 (q, *J* = 7 Hz) and δ 1.30 (t, *J* = 7 Hz) were assigned to its ethyl groups. In the mass spectrum, a molecular ion peak was observed at m/z 300.0855 corresponding to the formula $C_{14}H_{20}O_3S_2$. When DABCO was used, only the Michael adduct **16** was obtained in 65% yield along with the recovered starting material. The ir spectrum of compound **16** displayed a carbonyl absorption at 1715 cm^{-1} for the ketone and two bands at 1696 and 1665 cm^{-1} for the thiolesters. In the ^{1}H nmr spectrum, the two vinylic protons in the starting material disappeared, while the tosyl group was retained as indicated by the signals at δ 7.74 (m, 2 H), 7.30 (m, 2 H) and 2.40 (s, 3 H). The peaks at δ 2.90 (q, *J* = 7.5 Hz, 4 H) and 1.20 (t, *J* = 7.5 Hz, 6 H) were attributed to ethyl groups present in the thiomalonate moiety. The methine proton of this unit appeared at δ 3.60 as a doublet with a coupling constant of 10 Hz. The mass spectrum did not display the molecular ion peak. Instead, a peak appeared at m/z 349.0739 for the formula $C_{17}H_{17}O_6S$ due to the loss of an ethanethio radical and an ethanethiol unit from the molecular ion.

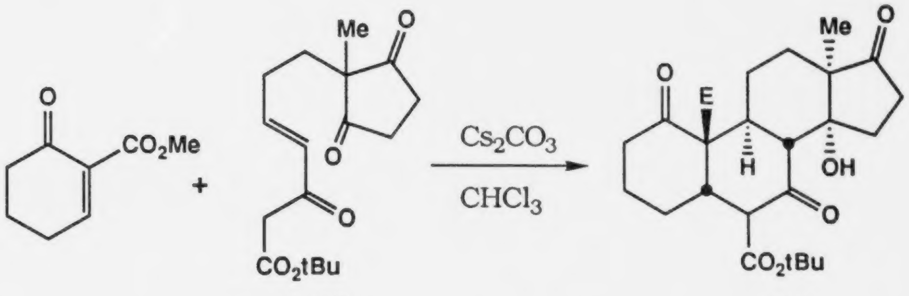
The alkylation product **15** could not be cyclized with DABCO in DME. On the other hand, when Michael adduct **16** was treated with sodium hydride in refluxing tetrahydrofuran (THF) in the presence of a catalytic amount (0.2 eq) of sodium iodide, the desired cyclization product **17** was formed, albeit in low yield (~ 10%) (Scheme 6). The ir spectrum of compound **17** showed a band at 1717 cm^{-1} for the ketone carbonyl and two absorptions at 1685 and 1660 cm^{-1} for the thiolesters. In the ^1H nmr spectrum, the signal corresponding to the methine proton of the thiomalonate moiety present in the starting material absent. Also absent were the signals for the tosyl group. The C_5 proton of **17** was observed as a broad singlet at a rather low field of δ3.43 due to the inductive effect of three carbonyls. The signals at δ2.90 (m, 4 H) and 1.26 (2 t, $J = 7$ Hz, 6 H) were assigned to the ethyl groups of the thiolesters. The mass spectrum displayed a molecular ion peak at m/z 300.0871, in agreement with the required molecular formula of $C_{14}H_{20}O_3S_2$.

The above results indicated the viability of the annelation process. However, the yield was far from satisfactory and the conditions employed could not effect the cyclization directly. Nevertheless, a number of conclusions can be drawn. First of all, the fact that sodium iodide could catalyze the reaction suggested that tosylate was not an adequate leaving group for the substitution step, and a better leaving group such as iodide ought to be used. Second, it appeared that the Michael addition was the key step to the success of the annelation process. The failure of sodium hydride to effect direct annelation could be attributed to the unfavorable reversible nature of the Michael reaction. This observation suggested that a proton source should be used to shift the equilibrium to the product formation.



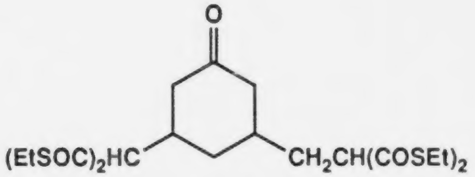
Scheme 6. i, NaH, DME; ii, DABCO, DME; iii, DABCO, DME; iv, NaH, THF, NaI.

The consideration of using alkoxide in the presence of the corresponding alcohol was ruled out in view of the unfavorable results obtained by Scheithauer and Mayer.[47] In their studies, sodium methoxide in methanol was used to induce the Michael addition of **7** to acrylonitrile and ethyl acrylate. Poor yields of 1,4-adducts were obtained. The combination of mercaptide and mercaptan represented another possibility. Unfortunately, mercaptide ion was known to undergo facile 1,4-addition reaction with α,β-unsaturated compounds. Its use in the present studies would be inappropriate. Since tertiary amines such as DABCO failed to effect the annelation, carbonates were then considered. Carbonate bases have been successfully used to induce both alkylations and Michael reactions of active methylene compounds. For example, sodium and potassium carbonate in the presence of tetraalkylammonium salts or crown ethers were used to effect alkylation reactions of active methylene compounds like diethyl malonate, ethyl cyanoacetate, etc., with a variety of electrophiles.[55] In a recent report by Deslongchamps and Lavallee,[56] cesium carbonate was employed to induce the polycyclization of 2-carbomethoxy-2-cyclohexenone with compound **18**, affording the tetracyclic compound **19** in a single operation. Therefore, carbonate bases could in principle meet the requirements for the cyclization. When a solution of iodo enone **14** and dithiomalonate **7** in acetone in the presence of potassium carbonate (2.5 eq) was stirred at room temperature for 51 h, to our delight, the annelation product **17** was obtained in 60% yield along with a small amount (8%) of compound **20**. The ir spectrum of **20** diplayed an intense carbonyl absorption at 1665-1690 cm^{-1}. The ^1H nmr spectrum showed the absence of vinylic protons. The signals at δ 3.76 (m, 1 H) and 3.55 (d, J = 7 Hz, 1 H) were attributed to the methine protons of the two thiomalonate moieties. In the mass spectrum, the molecular ion peak was not observed. However, the peak at m/z 431.1016 corresponding to the formula $C_{19}H_{27}O_5S_3$ was attributed to the loss of an ethanthio radical from the molecular ion.



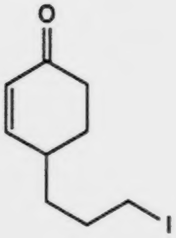
18 **19**

The above process was reproducible, and the cyclization product was obtained in 55-65% yield consistently. It was found that the rate of the cylization could be enhanced, as expected, by increasing the temperature to ca. 56°C (refluxing acetone). However, the yield of the desired product was inferior by 5-10%. The reactivity of tosylate **12** was studied by comparing with iodo enone **14**. It was observed that **12** reacted much slower (at least 5 times) than **14**.

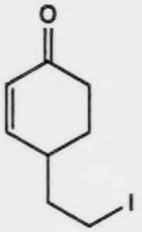


20

To test the generality of the above annelation process, iodo enones **21** and **22** were envisaged as suitable substrates. Their annelations with *S,S'*-diethyl dithiomalonate (**7**) would result in fused decalone and hydrindanone systems which are of broad synthetic utility.

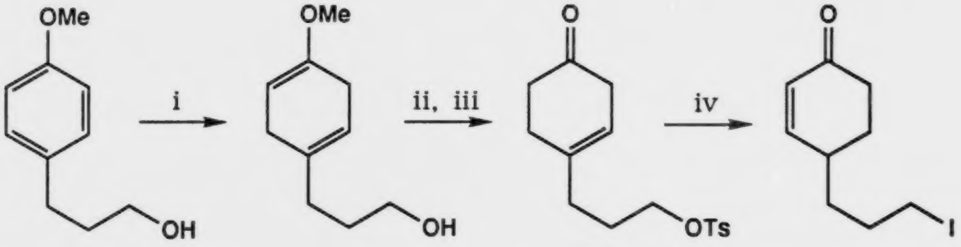


21



22

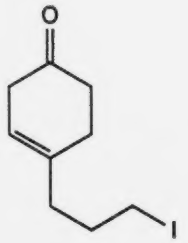
Iodo enone **21** was prepared from 3-(4-methoxyphenyl)-1-propanol (**23**) in overall 40% yield according to Scheme 7.



Scheme 7. i, Na, NH_3(l); ii, TsCl, TEA; iii, 0.1 N HCl; iv, NaI, acetone, reflux.

Birch reduction of **23**[57] followed by tosylation with tosyl chloride and triethylamine (TEA) in dichloromethane and hydrolysis of the tosylation product with aqueous hydrochloric acid afforded compound **24** in 80% yield. In the ir spectrum, compound **24** displayed a carbonyl absorption band at 1715 cm^{-1}. In the ^{1}H nmr spectrum, signals at δ 7.80 (m, 2H), 7.35 (m, 2 H) and 2.45 (s, 3 H) were attributed to the tosyl group. The vinylic proton appeared at δ 5.30 as a multiplet. The triplet at δ 4.05 (*J* = 6 Hz, 2 H) corresponded to the two methylene protons adjacent to the tosyl group. The molecular ion peak at m/z 308.1086 in the mass spectrum was consistent with the formula $C_{16}H_{20}O_4S$.

In the process of converting compound **24** to its corresponding iodide under Finkelstein reaction conditions,[54] two products were formed in a ratio of 5:8. The minor compound was identified as the normal substitution product **25** which showed a carbonyl absorption at 1715 cm^{-1} in the ir spectrum. In the ^1H nmr spectrum, the vinylic proton appeared at δ 5.50 as a multiplet. The signals for the tosyl group disappeared. A triplet (*J* = 6 Hz) at δ 3.15 was observed for the methylene protons adjacent to the iodo group. The molecular ion peak at m/z 264.0012 was in agreement with the formula $C_9H_{13}OI$.



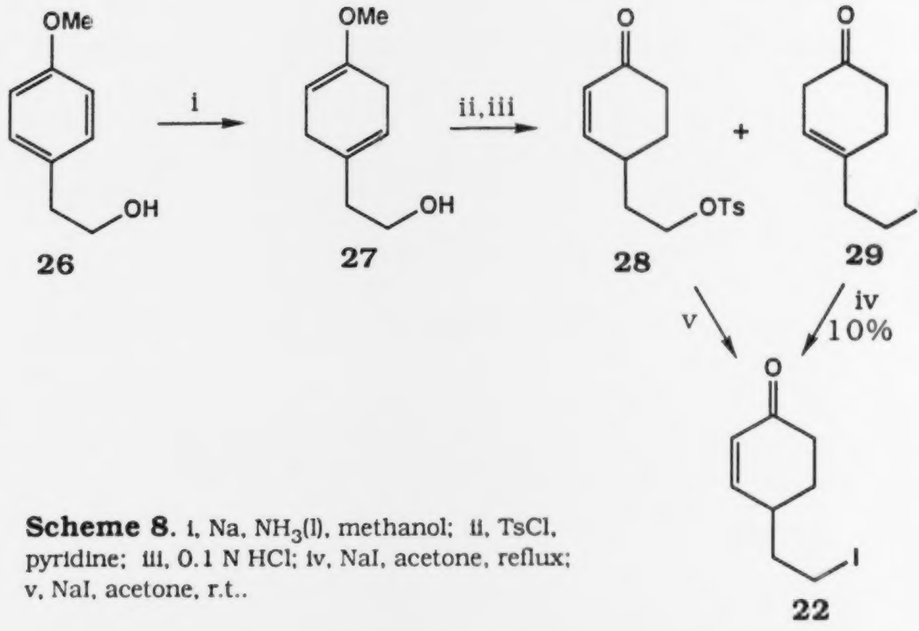
25

The major compound had a conjugated carbonyl absorption at 1678 cm^{-1} in the ir spectrum. The ^1H nmr spectrum showed two doublets of doublets at δ 6.85 (*J* = 10, 2 Hz, 1 H) and 6.00 (*J* = 10, 2 Hz, 1 H) confirming the presence of a conjugated enone system. In the mass spectrum, the molecular ion peak at m/z 264.0009 indicated the formula $C_9H_{13}OI$. Accordingly, the structure of the major product was assigned as the desired iodo enone **21**.

The above process was reproducible and it furnished iodo enone **21** in 50-55% yield consistently. Further treatment of iodo enone **25** with sodium iodide in refluxing acetone gave another 20-30% yield of **21**. These results were rather unexpected since sodium iodide was not known to isomerize β,γ-unsaturated ketones to the corresponding α,β-unsaturated isomers. However, a careful analysis suggested that the actual species which induced the isomerization might have been the trace amount of iodine present in the reaction system. Iodine has been used to isomerize double bonds to the corresponding thermodynamically more stable positions.[58]

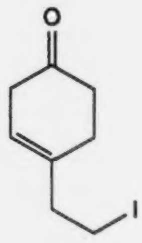
Attempts were then made to prepare iodo enone **22** in a similar fashion from 2-(4-methoxyphenyl)-1-ethanol (**26**) (Scheme 8). Birch reduction of **26** with sodium in liquid ammonia and methanol gave alcohol **27** in 95% yield. When **27** was tosylated with tosyl chloride in pyridine at 0°C for two days, followed by removal of pyridine in *vacuo* and direct hydrolysis of the residue by 1 N HCl, enones **28** and **29** were obtained in a 3 : 1 to 1 : 10 ratio. The ir spectrum of **28** displayed a conjugated carbonyl absorption at 1680 cm^{-1}. In the ^1H nmr spectrum, signals at δ 7.80 (m, 2 H), 7.35 (m, 2 H) and 2.40 (s, 3 H) were attributed to the tosyl group. Signals at δ 6.80 (dm, J = 10 Hz, 1 H) and 5.95 (dd, J = 10, 2 Hz, 1 H) confirmed the presence of a conjugated enone system. The signal at δ 4.20 (dd, J = 6, 6 Hz, 2 H) was assigned to the methylene protons adjacent to the tosyl group. The molecular ion peak in the mass spectrum appeared at m/z 294.0921, in agreement with the formula $C_{15}H_{18}O_4S$. Enone **29** showed a saturated ketone carbonyl absorption at 1715 cm^{-1}. In the ^1H nmr spectrum, the signals for the tosyl group appeared at δ 7.80 (m, 2H), 7.30 (m, 2 H) and 2.45 (s, 3 H). The vinylic proton appeared at δ 5.50 as a multiplet. The mass spectrum gave a molecular ion peak at 294.0918 corresponding to the formula $C_{15}H_{18}O_4S$.

Enone **28** was quantitatively transformed into the corresponding iodo enone **22** under Finkelstein reaction conditions.[54] The ir spectrum of **22** displayed a conjugated enone carbonyl absorption at 1676 cm^{-1}. In the ^1H nmr spectrum, the α- and β-protons of the enone moiety appeared at δ 6.02 (ddd, J = 10, 2.5, 0.5 Hz) and 6.80 (ddd, J = 10, 2.5, 1.5 Hz), respectively. The multiplet at δ 3.28 (2 H) was attributed to the methylene protons adjacent to the iodo group. In the mass spectrum, no molecular ion peak was observed. Instead, a peak at m/z 221.9540 corresponding to the formula C_6H_7OI was attributed to the loss of an ethylene unit from the molecular ion. The chemical ionization mass spectrum showed a $[M + NH_4]^+$ peak at 268.



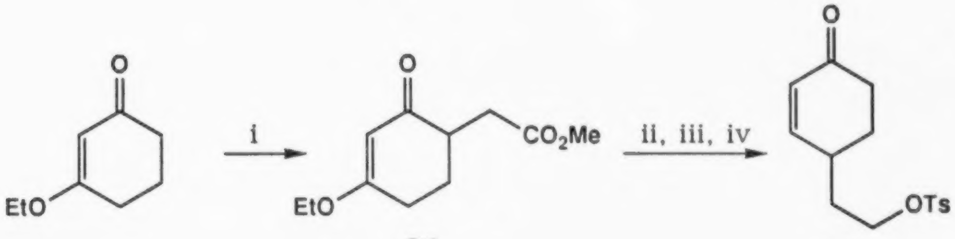
Scheme 8. i, Na, NH_3(l), methanol; ii, TsCl, pyridine; iii, 0.1 N HCl; iv, NaI, acetone, reflux; v, NaI, acetone, r.t..

When enone **29** was subjected to the same conditions employed previously for the isomerization of compound **25** to enone **21**, only a disappointing 10% yield of the desired enone **22** was obtained. The rest of the material, however, was not the expected enone **30**. In the ^{1}H nmr spectrum, it appeared to be a complicated mixture. Other attempts towards isomerizing enone **29** to its conjugated isomer **28** by using acid (p-TsOH), base (DBU) and $RhCl_3(H_2O)_3$[59] resulted in extensive decomposition of the starting material as indicated by TLC analysis.



30

The above route for the preparation of iodo enone **22** suffered from its low reproducibility. In some instances, the undesired isomer **29** was formed almost exclusively. Besides, how the conjugated enone **28** was formed during the tosylation and hydrolysis processes was not clear. Efforts made towards the isolation of the methyl enol ether before hydrolysis were fruitless. Consequently, a more reliable scheme was envisaged to prepare compound **28** (Scheme 9).

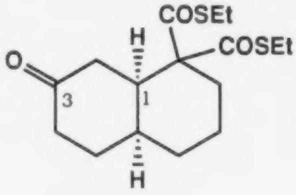


31 **28**

Scheme 9. i, *i*-Pr_2NLi, $BrCH_2CO_2Me$; ii, $LiAlH_4$; iii, TsCl, NaH; iv, 0.1 N HCl.

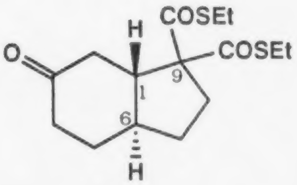
Stork-Danheiser alkylation[60] of 3-ethoxy-2-cyclohexenone with methyl bromoacetate and lithium diisopropylamide (LDA) followed by reduction with lithium aluminum hydride[61] gave crude compound **31**. Without purification, the primary hydroxy group was selectively tosylated with tosyl chloride and sodium hydride in THF. Subsequent hydrolysis with 1 N HCl afforded enone **28** in 30-40% yield consistently.

With enones **21** and **22** in hand, we then went on to study their annelation reactions with *S*,'*S*-diethyl dithiomalonate (**7**). When enone **21** was reacted with **7** in acetone in the presence of 2.5 eq of potassium carbonate at room temperature under an argon atmosphere for 43 h, the desired cyclization product **32** was obtained in 85% yield. The ir spectrum displayed a carbonyl absorption band at 1716 cm^{-1} and two absorption bands at 1698 and 1668 cm^{-1} for the thiolesters. In the ^1H nmr spectrum, the signal at δ 3.15 (ddd, J = 13.5, 4, 4 Hz, 1 H) was assigned to the angular H_1 methine proton β to the three carbonyls. A multiplet at δ 2.90 (4 H) and two triplets at δ 1.26 (J = 7 Hz, 3 H) and 1.24 (J = 7 Hz, 3 H) were attributed to the ethyl groups of the thiolesters. The molecular ion peak at m/z 328.1167 in the mass spectrum was in agreement with the required formula $C_{16}H_{24}O_3S_2$. The stereochemistry at the ring juncture was tentatively assigned to be *cis* based on the coupling pattern of the angular proton H_1 which showed a large coupling and two small couplings characteristic of an angular proton of a *cis*-fused decalone system.

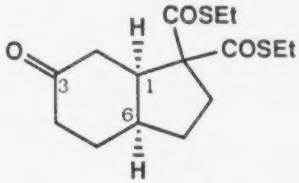


32

Similarly, when iodo enone **22** was stirred with **7** in acetone in the presence of potassium carbonate at room temperature for 36 h, two annelaton products were formed in a ratio of 1 : 46 and in a combined yield of 95% . The ir spectrum of the less polar minor product **33** displayed a carbonyl absorption at 1714 cm^{-1} and two absorption bands at 1680 and 1659 cm^{-1} for the thiolesters. In the ^1H nmr spectrum, the ethyl groups appeared at δ 2.93 (m, 4 H) and 1.27 (t, J = 7 Hz, 6 H). The molecular ion peak at m/z 314.1007 in the mass spectrum was consistent with the formula $C_{15}H_{22}O_3S_2$.



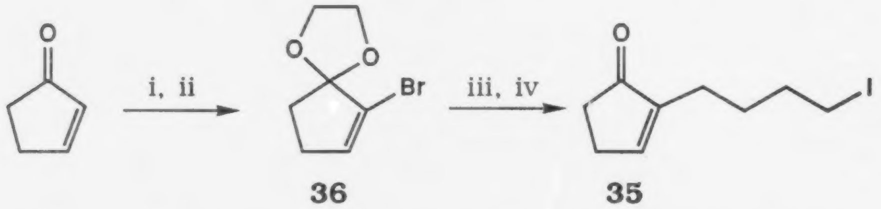
33



34

The ir spectrum of the major product **34** showed carbonyl absorption bands at 1717, 1686 and 1663 cm^{-1}. In the ^{13}C (APT) nmr spectrum, a total of 15 signals were observed. The ketone carbonyl carbon was at δ 211.47 and the thiolester carbonyl carbons appeared at δ 198.58 and 195.74. The C_9 quaternary carbon appeared at δ 79.89. The C_1 carbon and C_6 carbon appeared at δ 44.16 and 36.02, respectively. In the ^1H spectrum, the ethyl groups of the thiolesters appeared at δ 2.92 (m, 4 H), 1.27 (t, J = 7 Hz, 3 H) and 1.25 (t, J = 7 Hz, 3 H). The signal at δ 3.28 (ddd, J = 13, 6.5, 6 Hz) was determined to be the angular H_1 proton by an off-resonance decoupling experiment. Upon irradiating the proton signal at δ 3.28, the carbon signal at δ 44.16 became much sharper with a higher intensity. It could therefore be concluded that the proton at δ 3.28 was attached to the C_1 carbon. The *cis*-stereochemistry of the ring juncture was assigned according to the coupling pattern of the H_1 proton. The molecular ion peak at m/z 314.1003 and the elemental analysis were in full agreement with the formula $C_{15}H_{22}O_3S_2$ and the structure assigned.

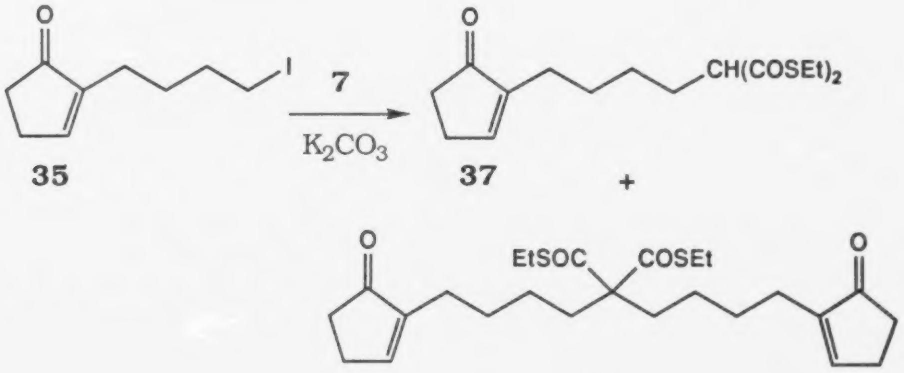
Attempts to extend the above annelation procedure to iodo enone **35** failed to furnish any cyclization products. Enone **35** was prepared according to Scheme 10. Bromination of 2-cyclopentenone followed by elimination of hydrogen bromide and subsequent protection of the ketone carbonyl group with ethylene glycol and *p*-TsOH yielded compound **36**.[62,63] Alkylation of **36** with 1,4-diiodobutane and *n*-BuLi followed by hydrolysis of the acetal with aqueous oxalic acid furnished enone **35**.[64]



Scheme 10. i, Br_2, CCl_4, then NEt_3; ii, ethylene glycol, *p*-TsOH, benzene; iii, *n*-BuLi, $I(CH_2)_4I$, THF; iv, 0.1 N oxalic acid, CH_2Cl_2.

When **35** was reacted with **7** in acetone in the presence of 2.5 eq of potassium carbonate, only the mono-alkylation and bis-alkylation products **37** and **38** were formed in a ratio of 3.8:1 in a combined yield of 95%. In the ^1H nmr spectrum of compound **37**, the vinylic proton appeared at δ 7.31 as a multiplet. The methine proton of the thiomalonate moiety appeared at δ 3.74 as a triplet with a coupling constant of 7 Hz. The quartet at δ 2.91 (*J* = 7 Hz, 4 H) and the triplet at δ 1.26 (*J* = 7 Hz, 6 H) were assigned to the ethyl groups of the thiolesters. The molecular ion peak in the mass spectrum was at m/z 328.1166, which was in agreement with the formula $C_{16}H_{24}O_3S_2$.

For compound **38**, the ^{1}H nmr spectrum indicated that the two cyclopentenone moieties were magnetically equivalent. The vinylic protons appeared at δ 7.31 as a multiplet. The quartet at δ 2.89 (*J* = 7 Hz, 4 H) and triplet at δ 1.23 (*J* = 7 Hz, 6 H) were attributed to the ethyl groups of the thiolesters. In the mass spectrum, the molecular ion was at m/z 464.2060 indicating the formula $C_{25}H_{36}O_4S_2$.



35 **37** **38**

The failure to obtain any annelation products in this particular instance could be attributed to the unfavorable nature of the

Michael addition process involving trisubstituted enones as observed by Liu and Oppong.[49] They found that the Michael reaction of **7** with either 2-methyl-2-cyclopentenone or 2-methyl-2-cyclohexenone did not take place.

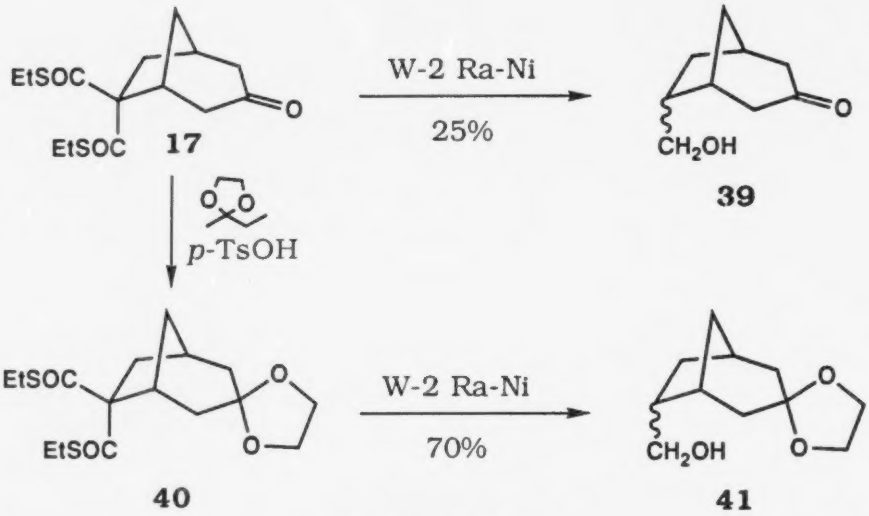
B. Reduction of the Annelation Products with W-2 Ra-Ni.

Having succeeded in the development of a procedure for the annelation reactions of *S,S'*-diethyl dithiomalonate (**7**) with appropriate ω-iodo enones, we turned our attention to the Ra-Ni reduction of the resulting cyclization products. It was anticipated based on the previous studies by Liu and coworkers[45,50] that the reduction of the dithiomalonate moiety in the cyclization products with Ra-Ni would lead to the removal of one thiolester group with the concomitant reduction of the other to the alcohol level. Liu and Oppong[50] have observed that when standard W-2 Ra-Ni was used, complications arose due to the transesterification of the thiolester with ethanol. Consequently, the Ra-Ni used in the present studies was prepared by washing with dilute acetic acid according to the procedure described by Liu and Oppong.[50]

Initial attempts to convert the dithiolester moiety of compound **17** to the ethanol unit directly with the acid washed W-2 Ra-Ni in benzene gave an unsatisfactory yield of 25% of the desired product **39** as a mixture of two inseparable diastereomers in a 3:1 ratio

(Scheme 11). The ir spectrum of compound **39** showed a broad absorption band at 3408-3442 cm^{-1} for the hydroxy group and a carbonyl absorption band at 1710 cm^{-1}. In the ^{1}H nmr spectrum, the methylene protons of the hydroxymethyl group for the major compound appeared at δ 3.57 (dd, J = 10.5, 7 Hz) and 3.48 (dd, J = 10.5, 9 Hz). For the minor isomer the methylene protons appeared at δ 3.36 (dd, J = 10.5, 7 Hz) and 3.29 (dd, J = 10.5, 9 Hz). The mass spectrum displayed a molecular ion peak at m/z 154.0996 corresponding to the formula $C_8H_{14}O_2$.

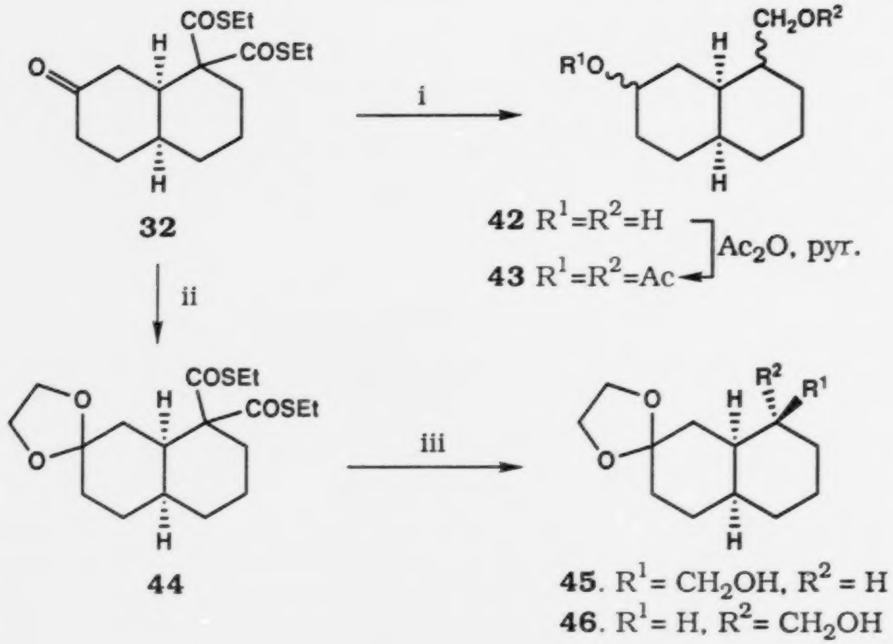
In order to improve the yield, ketone **17** was transformed into acetal **40** in 95% yield *via* a transacetalization process using 2-ethyl-2-methyl-1,3-dioxolane and a catalytic amount of *p*-TsOH in refluxing benzene. Acetal **40** showed a strong absorption band at 1667 cm^{-1} for the thiolesters in the ir spectrum. In the ^{1}H nmr spectrum, the multiplet at δ 3.65-3.92 (4 H) was attributed to the ethylene protons of the acetal moiety. The ethyl groups of the thiolesters were retained as indicated by the signals at δ 2.82-2.95 (m, 4 H), 1.26 (t, J = 7 Hz, 3 H) and 1.22 (t, J = 7 Hz, 3 H). The molecular ion peak at m/z 344.1115 in the mass spectrum was in agreement with the formula $C_{16}H_{24}O_4S_2$.



Scheme 11

Treatment of acetal **40** with excess Ra-Ni in benzene afforded an inseparable mixture of two epimeric alcohols **41** in a ratio of 9:1 and a combined yield of 70% (Scheme 11). The ir spectrum of compound **41** had a broad absorption at 3314-3360 cm^{-1} for the hydroxy group. In the ^1H nmr spectrum, the characteristic signals for the thiolesters disappeared. The multiplet at δ 3.88-4.02 (4 H) was attributed to the ethylene protons of the acetal moiety. The methylene protons of the hydroxymethyl group for the major compound appeared at δ 3.78-3.83 as multiplets, whereas the corresponding protons for the minor compound were found at δ 3.30-3.52 as multiplets. Finally the molecular ion peak at m/z 198.1253 in the mass spectrum and the elemental analysis were in full agreement with the formula $C_{11}H_{18}O_3$ and the structure assigned.

Treatment of compound **32** with excess Ra-Ni in benzene at room temperature for 5 h gave a very polar compound as indicated by TLC. The ir spectrum of the crude product indicated the absence of any carbonyl absorptions. A broad absorption band at 3321-3360 cm^{-1} indicated the presence of hydroxy groups. Accordingly, the product was assigned as diol **42**. To fully characterize the reduction product, the crude mixture was converted to the corresponding diacetate **43** by treatment with excess acetic anhydride in pyridine (Scheme 12). Flash chromatography separation gave two fractions in a ratio of 5:1 (by weight). The ir spectrum of the major fraction displayed a carbonyl absorption at 1740 cm^{-1}. The ^1H nmr spectrum was very complicated. However, the eight sharp lines at around δ 1.98, along with the four signals at δ 5.01, 4.48, 4.70 and 4.62 suggested that all four possible isomers were present. The mass spectrum did not give the molecular ion peak. However, the peak at m/z 225.1487 corresponded to the loss of one acetyl unit from the molecular ion. The base line at m/z 148.1253 was the result of two McLafferty rearrangements of the acetates. The minor fraction was not characterized due to the complexity of its spectral data.


COSEt
COSEt
H
O
H
32
i
CH2OR2
R1O
H
H
42 R1=R2=H
43 R1=R2=Ac
Ac2O, pyr.
ii
O
O
COSEt
COSEt
H
H
44
iii
R2
R1
H
H
45. R1= CH2OH, R2 = H
46. R1= H, R2= CH2OH

Scheme 12. i, Ra-Ni; ii, 2-ethyl-2-methyl-1,3-dioxolane, *p*-TsOH, or ethylene glycol, *p*-TsOH; iii, Ra-Ni.

The reduction of the ketone carbonyl group encountered in the present studies was not observed by Liu and Oppong[50] in their studies on the reduction of Michael adducts derived from *S,S'*-diethyl dithiomalonate (**7**). The complete reduction of the ketone carbonyl in our case may be attributed to the slow reduction, due to steric hindrance, of the thiolester groups in compound **32**. In order to circumvent this problem, compound **32** was protected in the form of acetal **44** *via* transacetalization with 2-ethyl-2-methyl-1,3-dioxolane and *p*-TsOH or by acetalization with ethylene glycol and *p*-TsOH in refluxing benzene with azeotropic removal of water. Both processes gave excellent yield of acetal **44**. The ir spectrum of **44** showed two carbonyl absorption bands at 1688 and 1666 cm^{-1}. In the ^1H nmr spectrum, the ethylene protons of the acetal moiety appeared at δ 3.90 as multiplets. The multiplets at δ 2.90 (4 H), and the two triplets at δ 1.24 (J = 7 Hz, 3 H) and 1.22 (J = 7 Hz, 3 H) were assigned to the ethyl groups of the thiolesters. In the mass spectrum, the molecular ion peak was found at m/z 372.1430, in agreement with the formula $C_{18}H_{28}O_4S_2$.

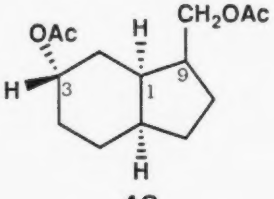
Treatment of acetal **44** with excess Ra-Ni in benzene at room temperature for 1 h gave a mixture two epimeric alcohols **45** and **46** in an approximately 1:1 ratio in 80% combined yield (Scheme 12). The two alcohols were readily separated by flash chromatography. The ir spectrum of compound **45** displayed a hydroxy absorption band at 3440 cm^{-1}. In the ^1H nmr spectrum, the four ethylene protons appeared at δ 3.94 as multiplets. The multiplets at δ 3.62 (2 H) were attributed to the methylene protons of the hydroxymethyl group. The molecular ion peak at m/z 226.1567 in the mass spectrum and the elemental analysis were in complete agreement with the formula $C_{13}H_{22}O_3$.

Compound **46** had a hydroxy absorption at 3429 cm^{-1} in the ir spectrum. In the ^1H nmr spectrum, the ethylene protons of the acetal moiety appeared at δ 3.94 as multiplets. The two doublets of doublets at δ 3.51 (J = 10.5, 7.5 Hz) and 3.42 (J = 10.5, 7 Hz) were attributed to the methylene protons of the hydroxymethyl group.

In the mass spectrum, the molecular ion was observed at m/z 226.1565 corresponding to the formula $C_{13}H_{22}O_3$. The elemental analysis also supported the structure assigned.

The stereochemistry of the hydroxymethyl group in each compound was tentatively assigned based on observed difference in chemical shifts, since the protons of the equatorial hydroxymethyl should have a lower chemical shift than those of the axial hydroxymethyl.[65]

As with compound **32**, direct reduction of compound **34** with Ra-Ni resulted in the complete reduction of the ketone carbonyl, giving diol **47** as a mixture of diastereomers (Scheme 13). The ir spectrum of **47** indicated the absence of any carbonyl absorption bands. The broad band at 3321-3356 cm^{-1} was attributable to the hydroxy groups. The ^1H nmr spectrum was very complicated in the region between δ 4.10 and 3.35. In the mass spectrum, the molecular ion was at m/z 170.1305 corresponding to the formula $C_{10}H_{18}O_2$. Acetylation of compound **47** with acetic anhydride in pyridine gave two diacetates in quantitative yield. Although only a single spot was observed on TLC, the ^1H nmr spectrum indicated the presence of two isomers in a ratio of 9:1. The minor compound **48** had a multiplet at δ 5.06, which was attributed to the H_3 equatorial proton. The H_3 axial proton for the major compound **49** appeared at δ 4.67 as a triplet of triplets (J = 11.5, 3.5 Hz). The methylene protons of the acetoxymethyl group for the major isomer appeared at δ 4.07 (dd, J = 11, 6.7 Hz) and 3.91 (dd, J = 11, 9 Hz). The molecular ion peak was not observed in the mass spectrum. However, the base peak at m/z 134.1099 corresponded to the loss of two acetic acid units from the molecular ion by two McLafferty rearrangements. The stereochemistry at C_9 for both compounds remains to be determined.



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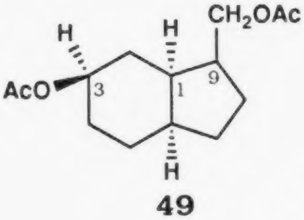


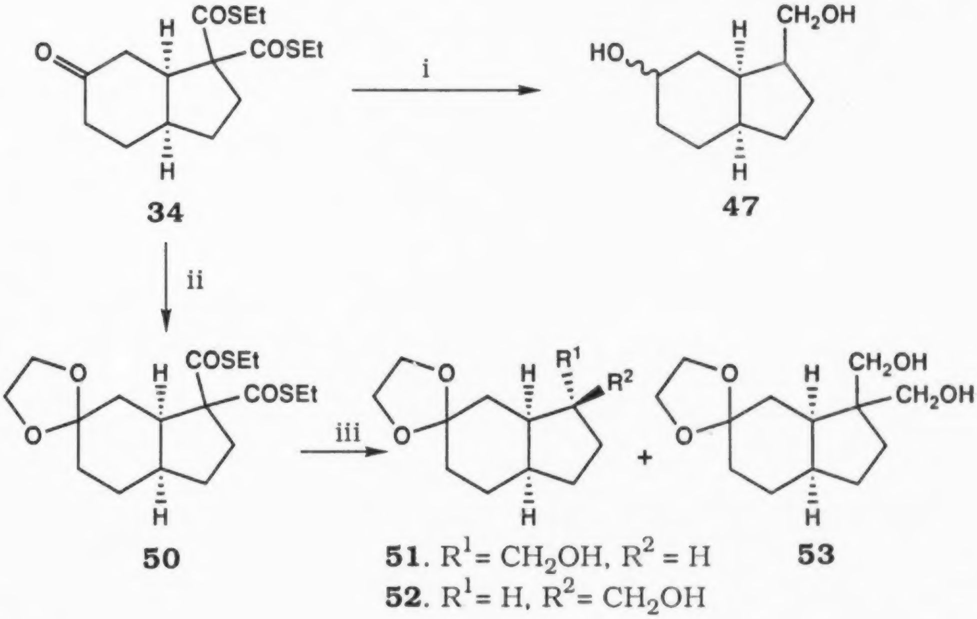
49

To prevent the reduction of the ketone carbonyl, compound **34** was converted to the corresponding acetal **50** in a similar manner as described previously for ketone **32**. Both methods afforded quantitative yields of acetal **50**. The ir spectrum showed two carbonyl absorption bands at 1688 and 1664 cm^{-1}. In the ^1H nmr spectrum, the ethylene protons for the acetal moiety was at δ 3.94 as multiplets. The signals at δ 2.83-2.95 (m, 4 H), 1.25 (t, J = 7 Hz, 3 H) and 1.22 (t, J = 7 Hz, 3 H) were attributed to the ethyl groups of the thiolesters. The mass spectrum displayed a molecular ion at m/z 358.1272 consistent with the formula $C_{17}H_{26}O_4S_2$.

Treatment of acetal **50** with an excess of the acid-washed W-2 Ra-Ni in benzene at room temperature for 2 h furnished a 70% yield of two epimeric alcohols **51** and **52** in a ratio of 1:3, along with a 20% yield of diol **53** (m.p. 169-170°C) (Scheme 13). For convenience, the minor alcohol was arbitrarily assigned to structure **51** and the major alcohol to **52**. For **51**, the ir spectrum had a hydroxy absorption at 3412 cm^{-1}. In the ^1H nmr spectrum, the multiplets at δ 3.94 (4 H) were assigned to the ethylene protons of the acetal moiety. The methylene protons of the hydroxymethyl group appeared at δ 3.45-3.70 as multiplets. The sharp singlet at 3.34 was attributed to the hydroxy proton. The molecular ion peak in the mass spectrum was at m/z 212.1417, in agreement with the formula $C_{12}H_{20}O_3$.

For **52**, the ir spectrum had a broad absorption at 3408 cm^{-1} for the hydroxy group. In the ^1H nmr spectrum, the multiplet at δ 3.94 (4 H) corresponded to the ethylene protons of the acetal moiety. The methylene protons of the hydroxymethyl group appeared at δ 3.50-3.60 as multiplets. The sharp singlet at δ 3.33 was attributed to the hydroxy proton. In the mass spectrum, the molecular ion was at m/z 212.1413 corresponding to the formula $C_{12}H_{20}O_3$. The stereochemistry for both alcohols remains to be assigned.

For diol **53**, the ir spectrum showed a broad absorption at 3250 cm^{-1} for the hydroxy groups. In the ^1H nmr spectrum (DMSO-d_6), two triplets at δ 4.46 (J = 5 Hz) and δ 4.30 (J = 4.5 Hz) were assigned to the two hydroxy protons. The ethylene protons of the acetal moiety appeared at δ 3.82 as multiplets. In the chemical ionization mass spectrum, the peak at m/z 260 corresponded to the $[M + NH_4]^+$ ion. The $[M + H]^+$ ion at m/z 243 and the molecular ion at m/z 242 were also observed.


COSEt
COSEt
O
H
H
34
i
HO
CH₂OH
H
H
47
ii
O
O
50
iii
R¹
R²
+
CH₂OH
CH₂OH
53
51. R¹= CH₂OH, R² = H
52. R¹= H, R²= CH₂OH

Scheme 13. i, Ra-Ni; ii, 2-ethyl-2-methyl-1,3-dioxolane, *p*-TsOH, or ethylene glycol, *p*-TsOH; iii, Ra-Ni.

As demonstrated in the above discussion, *S,S'*-diethyl dithiomalonate (**7**) can be applied effectively as a masked ethanol carbanion in annelation reactions. Its reaction with appropriate iodo enones allows cyclization with overall incorporation of an ethanol unit to give bridged and fused bicyclic compounds possessing functionalities suitable for further transformations.

Experimental

General

Melting points were recorded on a Kofler hot stage apparatus and are not corrected. Combustion elemental analyses were performed by the microanalytical laboratory of this department. Fourier transform infrared spectra were recorded on a Nicolet 7199 or Nicolet MX-1 FTIR spectrophotometer. Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a Bruker WH-80, Bruker WH-200, Bruker WH-300, Bruker WH-400 or Bruker AM-400 spectrometer using deuteriochloroform ($CDCl_3$) as solvent unless otherwise stated. Tetramethylsilane (TMS) was used as an internal reference. Coupling constants are reported to ± 0.5 Hz. Chemical shift measurements are reported in ppm downfield from TMS in delta (δ) units. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m= multiplet and br = broad. Carbon-13 nuclear magnetic resonance (^{13}C nmr) spectra were recorded on a Varian UNITY-500 (125 MHz) spectrometer, and were obtained as solutions in deuteriochloroform as the internal standard setting the central peak at 77.00 ppm. Carbon-13 multiplicities were derived from Carr-Purcell-Meiboom-Gill spin echo *J*-modulated experiments (APT or Attached Proton Test).[66,67] Methyl and methine groups are shown as signals possessing an antiphase (a) with respect to the deuteriochloroform signal, whereas methylene groups, quaternary carbons and carbonyl groups appear in phase (p) with it. High resolution electron impact mass spectra (hrms) were recorded using an A.E.I. model MS-50 mass spectrometer. Chemical ionization mass spectra (cims) were recorded on an A.E.I. MS-12 mass spectrometer, using ammonia as the reagent gas. Spectral data are reported as m/z values. Bulb-to-bulb distillation was performed using a Kugelrohr distillation apparatus. Concentrations of solvent systems used in column chromatography are given by volumes, e.g. 20% ethyl acetate in petroleum ether means 20 parts of ethyl acetate by volume to 80 parts of petroleum ether by volume.

Materials

Unless otherwise state, all materials used are commercially available. All compounds made are racemic. All reactions were carried out under a positive pressure of argon. Anhydrous reaction solvents were distilled under argon before use from the appropriate drying agents. Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were freshly distilled from a blue or purple solution of sodium benzophenone ketyl. Methanol was distilled from magnesium turnings. Acetone was predried with potassium carbonate, and then distilled from potassium carbonate. Alternatively, it was distilled from potassium permanganate, and then from potassium carbonate. Liquid ammonia was freshly distilled over sodium metal prior to use. Diisopropylamine was obtained by distillation from sodium metal. Pyridine and triethylamine (TEA) were distilled from calcium hydride. Benzene and ether were distilled from lithium aluminum hydride. Reactions requiring anhydrous conditions were performed in oven or flame-dried glassware, assembled and allowed to cool while being purged with argon. The term *in vacuo* refers to solvent removal *via* Buchi rotoevaporator at water aspirator pressure. Argon was passed through a column of 4 Å molecular sieves, with self indicating silica gel (coarse grained) as the indicator.

Flash chromatography developed by Still[68] was used routinely for purification and separation of product mixtures, using silica gel (Merck) of 230-400 mesh. All solvents were distilled prior to use for chromatography. Analytical thin layer chromatography (TLC) was carried out on aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck, Darmstadt). Ultraviolet active materials were detected by visualization under a uv lamp (254 or 350 nm). For TLC, the visualization of the chromatograms was completed by dipping in an ethanol solution of vanillin (5%, w/v) and sulfuric acid (5%, v/v), followed by careful charring on a hot plate. Alternatively, an aqueous solution of phosphomolybdic acid (3%, w/v) containing ceric sulfate (0.5%,w/v) and sulfuric acid (3%, v/v) was used as the dipping solution, followed by charring on a hot plate.

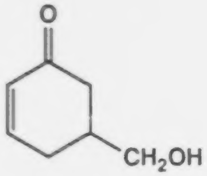
Modified W-2 Raney Nickel

A solution of sodium hydroxide (38 g) in distilled water (150 mL) was cooled in an ice bath to 5°C. Nickel-aluminum alloy (30 g) was added slowly with stirring. During the addition, the temperature of the mixture was not allowed to rise above 25°C. After the addition, the mixture was allowed to warm up to room temperature and was heated on a steam bath for 8 h. The solvent was decanted and the residue washed with distilled water (2 x 100 mL). A 10% aqueous sodium hydroxide solution (50 mL) was added. The mixture was stirred at room temperature for 20 min. After decanting the water, the residue was washed sequentially with distilled water (4 x 100 mL), 0.05 M aqueous acetic acid (4 x 100mL), water(4 x 120 mL), isopropyl alcohol (3 x 40 mL) and benzene (3 x 40 mL). The resulting Ra-Ni was stored in benzene or hexane.

S,S'-Diethyl dithiomalonate (7)

To a solution of malonyl dichloride (20.0 g, 0.14 mol) in ether (50 mL) under an argon atmosphere, was added dropwise a solution of ethanethiol (26.3 mL, 0.36 mol) in ether (50 mL). The mixture was stirred at room temperature for 10 min and cooled to 0°C. Pyridine (17.0 mL, 0.21 mol) in ether (50 mL) was then introduced slowly over a period of 10 min. The reaction mixture was allowed to warm up to room temperature and stirred for an additional 30 min. The solvent was removed *in vacuo* and the residue distilled under reduced pressure to afford the *S,S'*-diethyl dithiomalonate (**7**) (26.2 g, 99% yield) as a colorless oil: b.p. 100°C/2 torr; ir (film) 1680 and 1660 cm^{-1} (thiolesters); ^1H nmr δ 3.70 (s, 2H), 2.92 (q, *J* = 8 Hz, 4H), 1.24 (t, *J* =8 Hz, 6H); hrms M^+ 192.0277 (calcd. for $C_7H_{12}O_2S_2$: 192.0268).

5-(Hydroxymethyl)-2-cyclohexenone (13)

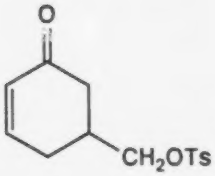


At -78°C, a solution of *m*-methoxybenzoic acid (5.0 g, 33.1 mmol) in methanol (45 mL) was added over a period of 15 min to freshly distilled ammonia (100 mL) under an argon atmosphere. Sodium metal (3.6 g, 0.16 g-atom) was added in small pieces over 10 min, and the resulting mixture was stirred vigorously for an additional 5 min. Ammonium chloride (15 g, 26.7 mmol) was then added. The mixture was allowed to warm up to room temperature and stirred for 4 h, allowing the ammonia to evaporate. The residue was dissolved in ice-cold water and the solution was cooled to 0°C. The solution was gradually adjusted to pH 4 at 0°C with concentrated HCl with frequent extractions into cold chloroform (4 x 30 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated to afford the crude reduced product (4.2

g). Without purification, the crude product (4.0 g) was dissolved in ether (30 mL) and the ethereal solution was added slowly to a suspension of lithium aluminum hydride (2.0 g, 58.8 mmol) in ether (30 mL) at 0°C under an atmosphere of argon. The mixture was stirred at room temperature overnight and cooled to 0°C. Water (0.26 mL, 14.7 mmol), 3 N aqueous sodium hydroxide (0.26 mL) and then water (0.52 mL) were added sequentially to the mixture. The resulting grey suspension was stirred at room temperature for 1 h. The mixture was filtered and the residue washed thoroughly with ether. The filtrate and washing solution were combined and concentrated to afford the crude product. To a solution of the crude product (3.0 g) dissolved in THF (25 mL) was added 1 N aqueous HCl (50 mL). The mixture was heated under reflux for 5 h and cooled to room temperature. Concentration *in vacuo* removed most of the THF and the remaining solution was extracted with dichloromethane (3 x 20 mL). The extracts were combined and washed with saturated sodium bicarbonate (15 mL). The organic solution was dried over magnesium sulfate, filtered and concentrated to afford the crude product which was subjected to column chromatography. Elution with a solution of ethyl acetate and dichloromethane (1:1) gave 5-(hydroxymethyl)-2-cyclohexenone (**13**) (2.5 g, 60% overall yield) as a colorless oil: ir ($CHCl_3$ cast) 3429 (br, OH) and 1673 cm^{-1} (C=O, enone); ^1H nmr (80 MHz) δ 6.90 (dm, J = 10 Hz, 1 H, -C**H**=CHCO-), 5.90 (br d, J = 10 Hz, 1 H, -CH=C**H**CO-), 3.50 (m, 2 H, -C$\mathbf{H}_2$OH), 2.80 (br s, 1 H,

-O**H**) and 2.10-2.50 (m, 5 H); hrms M$^+$ 126.0682 (calcd. for $C_7H_{10}O_2$: 126.0681).

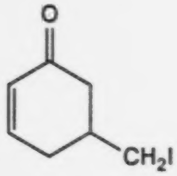
5-(Tosyloxymethyl)-2-cyclohexenone (12)



To a solution of 5-(hydroxymethyl)-2-cyclohexenone (249.7 mg, 1.98 mmol) and tosyl chloride (568.0 mg, 2.97 mmol) in dry dichloromethane (5 mL) under an argon atmosphere, were added pyridine (0.48 mL, 6.2 mmol) and a few crystals of 4,4-dimethylaminopyridine (DMAP). The mixture was stirred at room temperature for 24 h and poured into ice-cold 1 N HCl. The organic layer was separated and the aqueous layer extracted with dichloromethane (2 x 10 mL). The organic layer and extracts were combined and washed sequentially with ice-cold 1 N HCl (5 mL), water (5 mL), brine (5 mL) and dried over magnesium sulfate. The solvent was evaporated and the residue subjected to flash chromatography. Elution with ethyl acetate and hexane (40:60) afforded tosylate **12** (390 mg, 70% yield) as a flaky white solid. Recrystalization from ether and petroleum ether gave a white needle like crystal (m.p., 74-75°C, lit.[51] m.p., 74.5-75°C): ir ($CHCl_3$ cast) 1680 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz) δ 7.79 (m, 2 H, Ar**H**), 7.36 (m, 2 H, Ar**H**), 6.94 (ddd, J = 10, 3, 2.5 Hz, 1 H, -C**H**=CHCO-), 6.03 (dd, J = 10, 2.5 Hz, 1 H, -CH=C**H**CO-), 4.01 (dd,

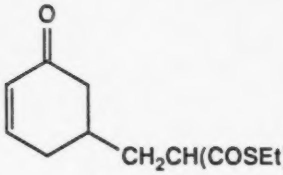
J = 9, 5 Hz, 1 H, -C**H**HOTs), 3.96 (dd, J = 9, 6 Hz, 1 H, -CH**H**OTs), 2.46 (s, 3H, -C**H**$_3$), 2.40-2.54 (m, 3 H) and 2.15-2.30 (m, 2 H); hrms M$^+$ 280.0767 (calcd. for $C_{14}H_{16}O_4S$: 280.0792).

5-(Iodomethyl)-2-cylohexenone (14)



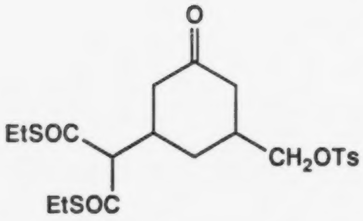
To a solution of tosylate **12** (136.3 mg, 0.487 mmol) in dry acetone (10 mL), was added sodium iodide (365.3 mg, 2.44 mmol). The mixture was heated to reflux with stirring for 3.5 h under an argon atmosphere and cooled to room temperature. Aqueous 10% sodium thiosulfate (5 mL) was added and the mixture was extracted with ether (3 x 15 mL). The extracts were combined and washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, filtered and concentrated to afford the crude product which was purified by flash chromatography. Elution with ethyl acetate and hexane (10:90) yielded iodo enone **14** (113 mg, 99% yield) as a colorless oil: ir (CH_2Cl_2 cast) 1679 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz) δ 6.97 (ddd, J = 10, 6, 2 Hz, 1 H, -C**H**=CHCO-), 6.00 (dm, J = 10 Hz, 1 H, -CH=C**H**CO-), 3.25 (m, 2 H, -C**H**$_2$I), 2.52-2.63 (m, 2 H) and 2.15-2.30 (m, 3 H); hrms M$^+$ 235.9709 (calcd. for C_7H_9OI: 235.9700).

S,S'-Diethyl 1-(5-oxo-3-cyclohexenyl)methyldithiomalonate (15)



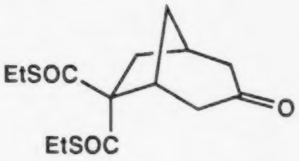
To a suspension of sodium hydride (80% dispersion in oil, 8.8 mg, 0.27 mmol) in DME (5 mL), were added **7** (52.4 mg, 0.27 mmol) in DME (1 mL) and tosylate **12** (68.2 mg, 0.24 mmol), followed by sodium iodide (35.7 mg, 0.24 mmol). The mixture was heated under reflux under an argon atmosphere for 3 h. After being cooled down to room temperature, the mixture was poured into ice cold 1 N HCl and extracted with dichloromethane (2 x 5 mL). The extracts were combined, washed with water, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by chromatography. Elution with ethyl acetate and hexane (20:80) afforded compound **15** (29.1 mg, 40% yield) as a colorless oil: ir ($CHCl_3$ cast) 1690-1666 cm^{-1} (C=O, enone and thiolesters); ^1H nmr (80 MHz) δ 7.01 (dm, *J* = 10 Hz, 1 H, -C**H**=CHCO-), 6.05 (br d, *J* = 10 Hz, 1 H, -CH=C**H**CO-), 3.25 (m, 1 H, -C**H**$(COSEt)_2$), 2.95 (q, *J* = 7 Hz, 4 H, 2 x -SC$\mathbf{H}_2$$CH_3$), 2.15-2.75 (m, 7 H) and 1.30 (t, *J* = 7 Hz, 6 H, 2 x -SCH_2C$\mathbf{H}_3$); hrms M^+ 300.0855 (calcd. for $C_{14}H_{20}O_3S_2$: 300.0854).

Compound (16)



To a solution of tosylate **12** (64.2 mg, 0.23 mmol) and *S,S'*-diethyl dithiomalonate (**7**) (53.0 mg, 0.28 mmol) in DME (3 mL), was added DABCO (31 mg, 0.28 mmol). The mixture was stirred at room temperature under an argon atmosphere for 3 days and poured into ice-cold 1 N HCl (5 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (2 x 5 mL). The organic layer and the extracts were combined, washed with water (5 mL) and brine (5 mL), dried over magnesium sulfate, filtered and concentrated to give the crude product which was purified by flash chromatography. Elution with ethyl acetate and hexane (20:80) afforded the Michael adduct **16** (67 mg, 62% yield) as a pale yellow oil: ir ($CHCl_3$ cast) 1715 (C=O, ketone), 1696 and 1665 cm^{-1} (C=O, thioleaters); ^1H nmr (80 MHz) δ 7.74 (d, J = 8 Hz, 2 H, Ar**H**), 7.30 (d, J = 8 Hz, 2 H, Ar**H**), 3.85 (br d, J = 6 Hz, 2 H, -C**H**$_2$OTs), 3.60 (d, J = 10 Hz, 1 H, -C**H**(COSEt)$_2$), 2.90 (q, J = 7 Hz, 4 H, 2 x -SC**H**$_2$CH$_3$), 2,40 (s, 3 H, -C**H**$_3$), 1.60-2.50 (m, 8 H) and 1.20 (t, J = 7 Hz, 6 H, 2 x -SCH$_2$C**H**$_3$); hrms m/z 349.0739 ($M^+-C_4H_{11}S_2$, calcd. for $C_{17}H_{17}O_6S$: 349.0746). Further elution gave the recovered starting material (10 mg, 16% yield).

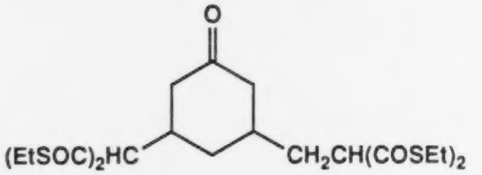
6,6-Bis(ethylthiocarbonyl)bicyclo[3.2.1]octan-3-one (17)



A. From Michael adduct **16**

To a suspension of sodium hydride (80% dispersion in oil, 6.7 mg, 0.22 mmol) in THF (3 mL), were added compound **16** (71.0 mg, 0.15 mmol) in THF (2 mL) and sodium iodide (4.5 mg, 0.03 mmol). The mixture was refluxed under argon for 11 h and cooled to room temperature. The mixture was then poured into ice-cold 1 N HCl (5 mL) and extracted with ether (3 x 10 mL). The extracts were combined, washed with water and brine, dried over magnesium sulfate and concentrated. Flash chromatography of the crude product using ethyl acetate and hexane (30:70) as eluent gave cyclization product **17** (10 mg, 22% yield) as a yellowish oil: ir ($CHCl_3$ cast) 1717 (C=O, ketone), 1685 and 1660 cm^{-1} (C=O, thiolesters); ^1H nmr (300 MHz) δ 3.43 (br s, 1 H), 2.82-3.01 (m, 4 H, 2 x -$SC\mathbf{H}_2CH_3$), 2.35-2.66 (m, 7 H), 1.92 (dddd, J = 7, 2.5, 2.5, 2.5 Hz, 1 H), 1.82 (br d, J = 7 Hz, 1 H), 1.26 (t, J = 7 Hz, 3 H, -$C\mathbf{H}_3$) and 1.25 (t, J = 7 Hz, 3 H, -$C\mathbf{H}_3$); hrms M^+ 300.0871 (calcd. for $C_{14}H_{20}O_3S_2$: 300.0854).

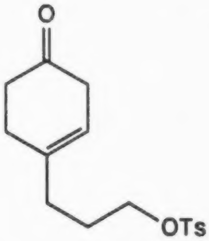
B. Compounds **17** and **20** from enone **14**



To a solution of 5-iodomethyl-2-cyclohexenone (**14**) (210 mg, 0.93 mmol) and *S,S'*-diethyl dithiomalonate (**7**) (270 mg, 1.41 mmol) in dry acetone (5 mL), was added potassium carbonate (321 mg, 2.32 mmol). The mixture was stirred at room temperature for 51 h under an argon atmosphere. Then water (5 mL) was added and the mixture extracted with ether (3 x 25 mL). The extracts were combined, washed with water (10 mL), brine (10 mL), dried over magnesium sulfate, filtered and concentrated to afford the crude product which was subjected to flash chromatography. Elution with ethyl acetate and hexane (10:90) gave the cyclization product **17** (180 mg, 67% yield) as a colorless oil.

Further elution with ethyl acetate and hexane (30:70) afforded ketone **20** (32 mg, 8% yield) as a viscous liquid: ir ($CHCl_3$ cast) 1715 (C=O, ketone), 1690-1665 cm^{-1} (br, C=O, thiolesters); ^{1}H nmr (300 MHz) δ 3.76 (m, 1 H, -CH$_2$C**H**(COSEt)$_2$), 3.55(d, *J* = 7 Hz 1 H, -C**H**(COSEt)$_2$), 2.93 (m, 8 H, 4 x -SC**H**$_2$CH$_3$), 2.72 (m, 1 H), 2.30-2.48 (m, 2 H), 2.05-2.20 (m, 2 H), 1.59-1.86 (m, 4 H), 1.23-1.34 (m, 13 H), 1.10 (m, 1 H); hrms m/z 432.1016 (M^+-C_2H_5S, calcd. for $C_{19}H_{27}O_5S_3$: 432.1020), also observed, 369.0827, 245.0457, 192.0283 and 177.0555 (base peak).

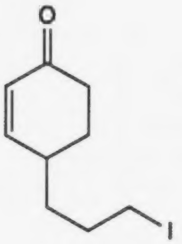
4-(3-Tosyloxypropyl)-3-cyclohexenone (24)



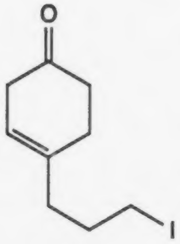
At -78°C, a solution of 3-(4-methoxyphenyl)-1-propanol (2.0 g, 12.0 mmol) in methanol (10 mL) was added to freshly distilled liquid ammonia (40 mL) over a period of 5 min under an argon atmosphere. Sodium metal (1.32 g, 0.057 g-atom) was added in small pieces over 5 min and the mixture was stirred vigorously at -78°C for 3 h. Then ammonium chloride (5 g, 93 mmol) was added. The mixture was allowed to warm up to room temperature, and stirred for 4 h, allowing the ammonia to evaporate. The residue was dissolved in ice-cold water (15 mL) and extracted with chloroform (3 x 50 mL). The extracts were combined, dried over magnesium sulfate, filtered and concentrated to afford the crude product (2.10 g) as a colorless oil: ^{1}H nmr (80 MHz) δ 5.45 (br s, 1 H, -C**H**=C-)), 4.65 (br s, 1 H, -C**H**=C(OMe)), 3.65 (t, *J* = 6 Hz, 2 H, $-C\mathbf{H}_2OH$), 3.55 (s, 3 H, $-OC\mathbf{H}_3$), 2.75 (br s, 4 H) and 1.50-2.25 (m, 5 H).

To a solution of the crude product (2.1 g) in dichloromethane (50 mL), were added TsCl (2.76 g, 14.4 mmol) and triethylamine (8.35 mL, 60 mmol). The mixture was then stirred at room temperature under an argon atmosphere for 18 h. After being cooled down to 0°C, the mixture was washed with 1 N HCl (2 x 15 mL). The organic layer was separated and mixed with 1 N HCl (50 mL). The resulting solution was stirred vigorously at room temperature for 5 h. The organic layer was separated, washed with water (10 mL) and brine (10 mL), and dried over magnesium sulfate. Filtration and concentration gave the crude product which was subjected to flash chromatography. Elution with ethyl acetate and hexane (30:70) afforded compound **24** (2.8 g, 76% overall yield) as a pale yellow oil: ir ($CHCl_3$ cast) 1715 cm^{-1} (C=O, ketone); ^1H nmr (80 MHz) δ 7.80 (m, 2 H, Ar**H**), 7.35 (m, Ar**H**), 5.30 (m, 1 H, -C**H**=C-), 4.05 (dd, *J* = 6, 6 Hz, 2 H, -C**H**$_2$OTs), 2.80 (br s, 2 H), 2.45 (s, 3 H, -C**H**$_3$) and 1.60-2.50 (m, 8 H); hrms M^+ 308.1086 (calcd. for $C_{16}H_{20}O_4S$: 308.1082).

4-(3-Iodopropyl)-2-cyclohexenone (21) and 4-(3-iodopropyl)-3-cyclohexenone (25)



21

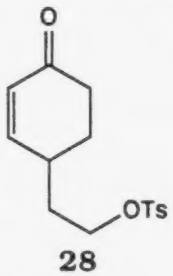


25

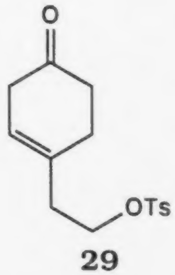
A solution of tosylate **24** (189 mg, 0.6 mmol) and sodium iodide (470 mg, 3.0 mmol) in actone (4 mL) was heated to reflux under an argon atmosphere for 4.5 h and cooled to room temperature. Half saturated sodium thiosulfate (5 mL) was added and the mixture was extracted with ether (3 x 10 mL). The extracts were combined, washed with water (5 mL) and brine (5 mL), and dried over magnesium sulfate. After filtration and concentration, the residue was subjected to flash chromatography. Elution with ethyl acetate and hexane (20:80) afforded iodo enone **25** (68 mg, 42% yield) as a colorless oil: ir (CHCl$_3$ cast) 1715 cm^{-1} (C=O, ketone); ^{1}H nmr (80 MHz) δ 5.50 (m, 1 H, -C**H**=C-), 3.15 (t, J = 6 Hz, 2 H, -C**H**$_2$I), 2.85 (br s, 2 H) and 1.40-2.60 (m 8 H); hrms M$^+$ 264.0012 (calcd. for C$_9$H$_{13}$OI: 264.0013).

Further elution gave enone **21** (89 mg, 55% yield) as a colorless oil: ir (CHCl$_3$ cast) 1679 cm^{-1} (C=O, enone); ^{1}H nmr (80 MHz) δ 6.85 (dd, J = 10, 2 Hz, 1 H, -C**H**=CHCO-), 6.00 (dd, J = 10, 2 Hz, 1 H, -CH=C**H**CO-), 3.20 (t, J = 6 Hz, 2 H, -C**H**$_2$I) and 1.45-2.70 (m, 9 H); hrms M$^+$ 264.0009 (calcd. for C$_9$H$_{13}$OI: 264.0013).

4-(2-Tosyloxyethyl)-2-cyclohexenone (28) and 4-(2-tosyloxyethyl)-3-cyclohexenone (29)



28



29

At -78°C, a solution of 2-(4-methyoxyphenyl)-1-ethanol (2.0 g, 13.1 mmol) in methanol (40 mL) was added to freshly distilled liquid ammonia (10 mL) over a period of 5 min under an argon atmosphere. Sodium metal (1.44 g, 0.063 g-atom) was added in small pieces over 5 min and the mixture was stirred vigorously at -78°C for 3 h. Then ammonium chloride (5 g, 93 mmol) was added and the mixture was allowed to warm up to room temperature, and stirred for 3 h, allowing the ammonia to evaperate. The residue was dissovled in ice-cold water (15 mL) and extracted with chloroform (3 x 50 mL). The extracts were combined, dried over magnesium sulfate, filtered and concentrated to afford the crude reduction product (2.00 g, 95% yield): ^{1}H nmr (300 MHz) δ 5.49 (br s, 1 H, -C**H**=C-), 4.62 (br s, 1 H, -C(OCH$_3$)=C**H**-), 3.68 (dd, *J* = 6, 6 Hz, 2 H, -C**H**$_2$OH), 3.55 (s, 3 H, -OC**H**$_3$), 2.75 (br s, 4 H), 2.27 (t, *J* = 6 Hz, 2 H, -C**H**$_2$CH$_2$OH) and 2.04 (br s, 1 H, -O**H**).

To a solution of the crude product (1.0 g, 6.5 mmol) in pyridine (15 mL), was added TsCl (1.49 g, 7.8 mmol). The mixture was stirred at 0°C under an argon atmosphere for 2 days. Most of the pyridine was removed on a Kugelrohr distillation apparatus and the residue was poured into ice-cold 1 N HCl (30 mL) and extracted with dichloromethane (3 x 20 mL). The extracts were combined, washed with 1 N HCl (20 mL) and water (20 mL), dried over magnesium sulfate, filtered and concentrated to give the crude product which was purified by flash chromatography. Elution with ethyl acetate and hexane (25:75) gave tosylate **29** (0.40 g, 20% yield) as a yellowish oil: ir (CHCl$_3$ cast) 1714 cm^{-1} (C=O, ketone); ^{1}H nmr (200 MHz) δ 7.78 (d, *J* = 8 Hz, 2 H, Ar**H**), 7.36 (d, *J* = 8 Hz, 2 H, Ar**H**), 5.49 (m, 1 H, -C**H**=C-), 4.14 (t, *J* = 7 Hz, 2 H,

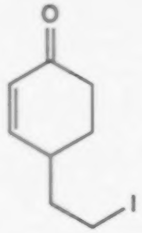
-C**H**$_2$OTs), 2.82 (br s, 2 H), 2.47 (s, 3 H, -C**H**$_3$), 2.43 (m, 2 H), 2.32 (m, 2 H), 1.98 (m, 1 H) and 1.66 (m, 1 H); hrms M$^+$ 294.0933 (calcd. for $C_{15}H_{18}O_4S$: 294.0926).

Further elution using ethyl acetate and hexane (40:60) gave tosylate **28** (0.70 g, 34% yield) as a pale yellow oil: ir ($CHCl_3$ cast) 1680 cm^{-1} (C=O, enone); ^{1}H nmr (80 MHz) δ 7.80 (m, 2 H, Ar**H**), 7.35 (m, 2 H, Ar**H**), 6.80 (dm, *J* = 10 Hz, 1 H, -C**H**=CHCO-), 5.95 (dd, *J* = 10, 2 Hz, 1 H, -CH=C**H**CO-), 4.20 (dd, *J* = 6, 6 Hz, 2 H, -C**H**$_2$OTs), 2.40 (s, 3 H, -C**H**$_3$) and 1.40-2.70 (m, 7 H); hrms M$^+$ 294.0921 (calcd. for $C_{15}H_{18}O_4S$: 294.0926).

Enone 28 by Stork-Danheiser alkylation method

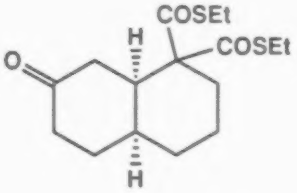
To a solution of diisopropylamine (3.36 mL, 24.0 mmol) in THF (20 mL) at 0°C under an argon atmosphere, was added dropwise *n*-BuLi (8.8 mL, 2.5 M in hexane). The mixture was stirred at 0°C for 15 min and cooled down to -78°C. A solution of 3-ethoxy-2-cyclohexenone (2.80 g, 20.0 mmol) in THF (10 mL) was introduced over a period of 10 min to the above LDA solution, and the mixture was stirred at -78°C for 1 h. Then methyl bromoacetate (3.8 mL, 40.0 mmol) was added in one portion, and the resulting reaction mixture was allowed to warm up slowly to room temperature (4 h) and stirred overnight. After being cooled to 0°C, saturated ammonium chloride (40 mL) was added and the mixture was extracted with ether (3 x 40 mL). The extracts were combined, washed with water (3 x 30 mL) and brine (30 mL), dried over magnesium sulfate and concentrated to afford the crude product. Vacuum distillation at 105-110°C/1 torr using a Kugelrohr apparatus afforded the crude alkylation product which was reduced without further purification. A solution of the crude product (2.2 g) in THF (15 mL) was added to a suspension if lithium aluminum hydride (0.8 g, 20.8 mmol) in THF (20 mL) at 0°C under an argon atmosphere over a period of 15 min. The mixture was stirred at room temperature overnight and cooled to 0°C. Then water (0.4 mL, 22 mmol), 3 N sodium hydroxide (0.4 mL), water (0.8 mL) were added cautiously over a period of 1 h. The resulting grey suspension was stirred at room temperature for 3 h and filtered. The residue was washed thoroughoutly with ether. The organic solutions were combined, dried over magnesium sulfate, filtered and concentrated to afford the crude reduction product. To a suspension of sodium hydride (60% dispersion in oil, 0.39 g, 9.75 mmol) in THF (15 mL) at 0°C under an argon atmosphere, was added a solution of the crude reduction product (1.63 g) in THF (10 mL) over a period of 10 min. The mixture was stirred at 0°C for 1 h and then TsCl (4.2 g, 21.9 mmol) was introduced. The resulting mixture was stirred at room temperature for 24 h. Then 1 N HCl (30 mL) was added. The solution was stirred for another 3 h and extracted with ether (3 x 40 mL). The extracts were combined, washed with water (30 mL) and brine (30 mL), and dried over magnesium sulfate. The solution was filtered and concentrated to give the crude product which was subjected to flash chromatography. Elution with ethyl acetate and hexane (40:60) afforded compound **28** (2.0 g, 31% overall yield) as a pale yellow oil.

4-(2-Iodoethyl)-2-cyclohexenone (22)



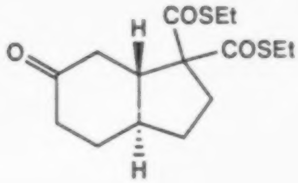
A solution of tosylate **28** (800 mg, 2.72 mmol) and sodium iodide (4.0 g, 27.2 mmol) in acetone (15 mL) was stirred at room temperature under an argon atmosphere for 2 h. Then water and 10% sodium thiosulfate (5 mL each) were added and the mixture was extracted with ether (3 x 15 mL). The extracts were combined and washed with water (10 mL) and brine (10 mL). The organic solution was dried over magnesium sulfate, filtered and concentrated. Flash chromatography using ethyl acetate and hexane (20:80) as eluent afforded iodo enone **22** (0.66 g, 98% yield) as a colorless oil: ir (film) 1676 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz) δ 6.80 (ddd, *J* = 10, 2.5, 1.5 Hz, 1 H, -C**H**=CHCO-), 6.02 (ddd, *J* = 10, 2.5, 0.5 Hz, 1 H, -CH=C**H**CO-), 3.20-3.36 (m, 2 H, -C**H**$_2$I), 2.53 (m, 1 H), 2.52 (dt, *J* = 17, 5 Hz, 1 H), 2.41 (ddd, *J* = 14, 14, 5 Hz, 1 H), 2.02-2.21 (m, 2 H), 1.90 (m, 1H) and 1.68 (m, 1 H); hrms m/z 221.9540 ($M^+-C_2H_4$, calcd. for C_6H_7OI: 221.9543); cims $[M + NH_4]^+$ 268.

(1R*,6S*)-10,10-Bis(ethylthiocarbonyl)bicyclo[4.4.0]decan-3-one (32)

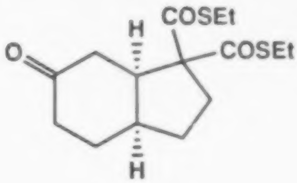


A solution of 4-(3-iodopropyl)-2-cyclohexenone (**21**) (189.4 mg, 0.718 mmol), *S,S'*-diethyl dithiomalonate (**7**) (210 mg, 1.08 mmol) and potassium carbonate (197 mg, 2.15 mmol) in acetone (8 mL) was stirred at room temperature under an argon atmosphere for 43 h. Then water (5 mL) was added and the mixture was extracted with ether (3 x 15 mL). The extracts were combined and washed with water (5 mL) and brine (5 mL). The soluton was dried over magnesium sulfate, filtered and concentrated to yield the crude product which was purified by flash chromatography. Elution with ethyl acetate and hexane (20:80) afforded the annelation product **32** (201 mg, 85% yield) as a colorless oil: ir ($CHCl_3$ cast) 1716 (C=O, ketone), 1698 and 1668 cm^{-1} (C=O, thiolesters); ^1H nmr (400 MHz) δ 3.15 (ddd, J = 13.5, 4, 4 Hz, 1 H), 2.90 (m, 4 H, 2 x $-SC\mathbf{H}_2CH_3$), 2.25-2.42 (m, 4 H), 2.00-2.10 (m, 3 H), 1.84-1.98 (m, 3 H), 1.40-1.71 (m, 3 H), 1.26 (t, J = 7 Hz, 3 H, $-SCH_2C\mathbf{H}_3$) and 1.24 (t, J = 7 Hz, 3 H, $-SCH_2C\mathbf{H}_3$); hrms M^+ 328.1167 (calcd. for $C_{16}H_{24}O_3S_2$: 328.1167).

(1S*, 6S*)-9,9-Bis(ethylthiocarbonyl)bicyclo[4.3.0]nonan-3-one (33) and (1R*, 6S*)-9,9-bis(ethylthiocarbonyl)bicyclo[4.3.0]nonan-3-one (34)



33

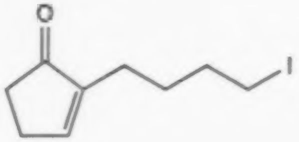


34

To a solution of iodo enone **22** (410 mg, 1.64 mmol) and *S,S'*-diethyl dithiomalonate (**7**) (479 mg, 2.46 mmol) in acetone, was added potassium carbonate (570 mg, 4.1 mmol). The mixture was stirred at room temperature under an argon atmosphere for 36 h. Then water (5 mL) was added and the mixture was extracted with ether (3 x 15 mL). The extracts were combined , washed with saturated ammonium chloride (10 mL) and brine (10 mL), dried over magnesium sulfate, filtered and concentrated to give the crude product which was subjected to flash chromatography. Elution with ethyl acetate and hexane (7:93) afforded the minor annelation product **33** (10 mg, 2% yield) as a colorless oil: ir (CH_2Cl_2 cast) 1714 (C=O, ketone), 1680 and 1659 cm^{-1} (C=O, thiolester); ^1H nmr (300 MHz) δ 2.93 (m, 4 H, 2 x -$SC\mathbf{H}_2CH_3$), 2.85 (ddd, J = 13, 2, 2 Hz, 1 H), 2.69 (ddd, J = 14.5, 8.5, 8.5 Hz, 1 H), 2.01-2.44 (m, 9 H), 1.40 (m, 1 H) and 1.27 (t, J = 7 Hz, 6 H, 2 x -$SCH_2C\mathbf{H}_3$); hrms M^+ 314.1007 (calcd. for $C_{15}H_{22}O_3S_2$: 314.1010).

Further elution gave the major cyclization product **34** (472 mg,92% yield) as a colorless oil: ir (CH_2Cl_2 cast) 1717 (C=O, ketone), 1686 and 1663 cm^{-1} (C=O, thiolesters); ^{1}H nmr (300 MHz) δ 3.28 (ddd, *J* = 13, 6.5, 6 Hz, 1 H,), 2.86-2.99 (m, 5 H), 2.60 (ddd, *J* = 14, 9, 9 Hz, 1 H), 2.32-2.48 (m, 4 H), 2.13-2.23 (m, 2 H), 1.65-2.06 (m, 5 H), 1.27 (t, *J* = 7 Hz, 3 H, -$SCH_2C\mathbf{H}_3$) and 1.25 (t, *J* = 7 Hz, 3 H, -$SCH_2C\mathbf{H}_3$); ^{13}C nmr (125 MHz, APT) δ 211.47 (p, **C**=O, ketone), 198.58 (p, **C**=O, thiolester), 195.74 (p, **C**=O, thiolester), 79.88 (p, $\mathbf{C}_9$), 44.16 (a, $\mathbf{C}_1$), 38.79 (p), 37.22 (p), 36.02 (a, $\mathbf{C}_6$), 30.26 (p), 27.92 (p), 26.75 (p), 24.17 (p), 24.03 (p), 14.29 (a, $\mathbf{C}H_3$) and 14.22 (a, $\mathbf{C}H_3$); hrms M$^+$ 314.1003 (calcd. for $C_{15}H_{22}O_3S_2$: 314.1010). Anal. calcd. for $C_{15}H_{22}O_3S_2$: C 57.29, H 7.05, S 20.39; found: C 57.24, H 7.18, S 20.49.

2-(4-Iodobutyl)-2-cyclopentenone (35)



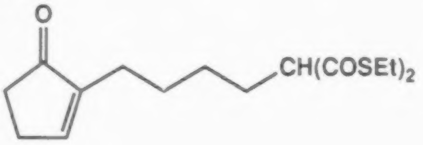
To a solution of 2-cyclopentenone (4.0 g, 48.8 mmol) in CCl_4 (40 mL) at 10°C, was added bromine (2.50 mL, 48.8 mmol) in CCl_4 (40 mL) rapidly in 2 min. Then triethylamine (24 mL, 170 mmol) was introduced and the resulting milky mixture was stirred at room temperature for 4 h and then filtered. The filtrate was washed with 1 N HCl (30 mL) and water (30 mL), dried over magnesium sulfate, filtered and concentrated to afford the crude 2-bromo-2-

cyclopentenone. Bulb-to-bulb distillation (55-60°C/0.6-0.7 torr) gave the pure product (5.02 g) as a colorless oil. The ^1H nmr spectrum was identical with the reported.[62,63] A mixture of 2-bromo-2-cyclopentenone (4.4 g, 27.0 mmol), ethylene glycol (2.3 mL, 41.0 mmol) and *p*-TsOH (30 mg, 0.14 mmol) in benzene (80 mL) was heated under reflux under argon for 24 h with azeotropic removal of water. After being cooled down to room temperature, the mixture was washed with 5% sodium carbonate (10 mL) and water (2 x 20 mL) and dried over magnesium sulfate. Filtration and concentration gave the crude product which was purified by flash chromatography. Elution with ethyl acetate and hexane (10:90) gave the pure 2-bromo-2-cyclopentenone ethylene acetal **36** (3.8 g) and starting material (1.0 g). The ^1H nmr spectrum of the acetal was identical with that reported.[62,63] To a mixture of the acetal (0.5 g, 2.44 mmol) in THF (20 mL) at -78°C, was added *n*-BuLi (1.3 mL of 2.2 M solution in hexane, 2.93 mmol) under an argon atmosphere. The mixture was stirred at -78°C for 1 h and then 1,4-diiodobutane (1.66 g, 5.36 mmol) in THF (7 mL) was introduced dropwise. The mixture was stirred at room temperature for 18 h. Saturated ammonium chloride (20 mL) was added and the mixture was extracted with ether (3 x 20 mL). The extracts were combined, washed with water and brine, and dried over magnesium sulfate. Filtratration and concentration gave the crude product which was subjected to flash chromatography. Elution with ethyl acetate and hexane (5:95) gave 2-(4-iodobutyl)-2-

cyclopentenone ethylene acetal (0.45 g, 60% yield) as a colorless oil: ^{1}H nmr (200 MHz) δ 5.73 (m, 1 H, -C**H**=C-), 3.95 (m, 4 H, -OC**H**$_2$C**H**$_2$O-), 3.20 (t, *J* = 7 Hz, 2 H, -C**H**$_2$I), 2.30 (m, 2 H), 1.95-2.04 (m, 4 H), 1.88 (m, 2 H) and 1.65 (m, 2 H); hrms M$^+$ 308.0276 (calcd. for $C_{11}H_{17}O_2I$: 308.0275).

To a solution of the above acetal (0.4 g, 1.3 mmol) in dichloromethane (15 mL), was added oxalic acid (0.52 g) in water (13 mL). The mixture was stirred at room temperature for 20 h. The organic layer was separated and washed with saturated sodium bicarbonate (5 mL) and water (5 mL). The organic solution was concentrated to afford the crude product which was purified by chromatography. Elution with ethyl acetate and hexane (20:80) gave enone **35** (0.32 g, 95% yield) as a colorless oil: ir ($CHCl_3$ cast) 1690 cm^{-1} (C=O, enone); ^{1}H nmr (200 MHz) 7.35 (m, 1 H, -C**H**=CCO-), 3.19 (t, *J* = 7 Hz, 2 H, -C**H**$_2$I), 2.60 (m, 2 H), 2.42 (m, 2 H), 2.10 (m, 2 H), 1.85 (m, 2 H) and 1.63 (m, 2 H); hrms M$^+$ 264.0011 (calcd. for $C_9H_{13}OI$: 264.0013).

Compounds 37 and 38



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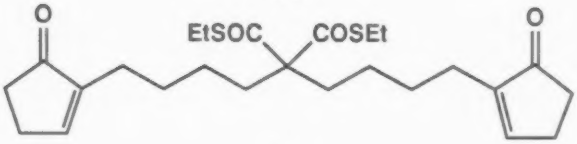
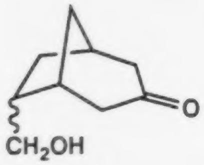


38

To a solution of iodo enone **35** (141.5 mg, 0.536 mmol) and *S,S'*-diethyl dithiomalonate (**7**) (130 mg, 0.677 mmol) in acetone (5 mL), was added potassium carbonate (185 mg, 1.34 mmol). The mixture was stirred at room temperature under an argon atmosphere for 39 h. Then water (5 mL) was added and the mixture was extracted with ether (3 x 10 mL). The extracts were combined, washed with water (5 mL) and brine (5 mL), dried over magnesium sulfate, filtered and concentrated to give the crude product which was purified by flash chromatography. Elution with ethyl acetate and hexane (20:80) afforded the mono-alkylation product **37** (132 mg, 75% yield) as a colorless oil: ^{1}H nmr (300 MHz) δ 7.31 (m, 1 H, -C**H**=CCO-), 3.74 (t, *J* = 7 Hz, 1 H, -C**H**(COSEt)$_2$), 2.91 (q, *J* = 7 Hz, 4 H, 2 x -SC**H**$_2$CH$_3$), 2.56 (m, 2 H), 2.39 (m, 2 H), 2.17 (m, 2 H), 1.97 (dd, *J* = 7 Hz, 2 H), 1.50 (quin, *J* = 7 Hz, 2 H), 1.34 (m, 2 H) and 1.26 (t, *J* = 7 Hz, 6 H, 2 x -SCH$_2$C**H**$_3$); hrms M$^+$ 328.1166 (calcd. for $C_{16}H_{24}O_3S_2$: 328.1167).

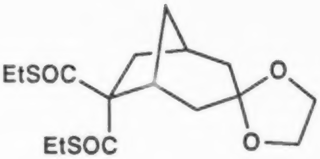
Further elution with ethyl acetate and hexane (50:50) gave compound **38** (43 mg, 17.3% yield) as a colorless oil: ^{1}H nmr (300 MHz) δ 7.31 (m, 2 H, 2 x -C**H**=CCO-), 2.89 (q, *J* = 7 Hz, 4 H, 2 x -SC**H**$_2$CH$_3$), 2.56 (m, 4 H), 2.39 (m, 4 H), 2.17 (m, 4 H), 2.20 (m, 4 H), 1.50 (quin, *J* = 7 Hz, 4 H), 1.23 (t, *J* = 7 Hz, 6 H, 2 x -SCH$_2$C**H**$_3$) and 1.18 (m, 4 H); hrms M$^+$ 464.2060 (calcd. for $C_{25}H_{36}O_4S_2$: 464.2055).

6-(Hydroxymethyl)bicyclo[3.2.1]octan-3-one (39)



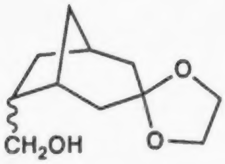
To a suspension of W-2 Ra-Ni (0.5 mL, settled volume) in benzene (3 mL) under an argon atmosphere, was added compound **17** (55 mg, 0.183 mmol) in benzene (2 mL). The mixture was stirred at room temperature for 24 h and filtered. The residue was washed thoroughly with benzene (2 x 5 mL), benzene and ethanol (1:1, 2 x 5 mL) and ethanol (2 x 5 mL). The filtrate and washing solutions were combined and concentrated to give the crude product which was purified by flash chromatography. Elution with ethyl acetate and hexane (60:40) afforded alcohol **39** (3:1 mixture of two diastereomers, 6.6 mg, 23.4% yield) as a colorless oil: ir ($CHCl_3$ cast) (br, 3420 OH), 1710 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz) δ 3.57 (dd, J = 10.5, 7 Hz, 1 H) and 3.48 (dd, J = 10.5, 9 Hz, 1 H) for the major compound; δ 3.36 (dd, J = 10.5, 7 Hz, 1 H) and 3.29 (dd, J = 10.5, 9 Hz, 1 H) for the minor compound; the rest of the protons appeared at δ 0.92-2.50; hrms M^+ 154.0996 (calcd. for $C_9H_{14}O_2$: 154.0994).

6,6-Bis(ethylthiocarbonyl)-3,3-ethylenedioxybicyclo[3.2.1]octane (40)



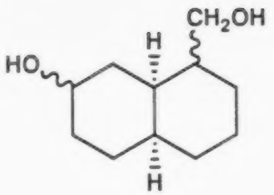
A solution of compound **17** (130 mg, 0.433 mmol), 2-ethyl-2-methyl-1,3-dioxolane (1.6 mL) and *p*-TsOH (8.2 mg, 0.043 mmol) in benzene (25 mL) was heated to reflux under an argon atmosphere for 24 h. After being cooled down to room temperature, the mixture was washed with half saturated sodium bicarbonate (5 mL) and brine (5 mL), dried over magnesium sulfate, filtered and concentrated to afford the crude product which was subjected to flash chromatography. Elution with ethyl acetate and hexane (10:90) gave acetal **40** (120 mg, 80% yield) as a colorless oil: ir ($CHCl_3$ cast) 1667 cm^{-1} (br, C=O, thiolesters); ^1H nmr (300 MHz) δ 3.65-3.92 (m, 4 H, $-OC\mathbf{H}_2C\mathbf{H}_2O-$), 3.04 (dd, J = 7, 3 Hz, 1 H), 2.82-2.95 (m, 5 H, 2 x $-SC\mathbf{H}_2CH_3$), 2.63 (dd, J = 13.5, 2 Hz, 1 H), 2.57 (dm, J = 13.5 Hz, 1 H), 2.43 (m, 1 H), 1.87 (dd, J = 14, 3.2 Hz, 1 H), 1.80 (dddd, J = 14, 2, 2, 2 Hz, 1 H), 1.57 (dd, J = 14, 3.2 Hz, 1 H), 1.54 (m, 1 H), 1,41 (br d, J = 11.5 Hz, 1 H), 1.26 (t, J = 7 Hz, 3 H, $-SCH_2C\mathbf{H}_3$) and 1.22 (t, J = 7 Hz, 3 H, $-SCH_2C\mathbf{H}_3$); hrms M^+ 344.1115 (calcd. for $C_{16}H_{24}O_4S_2$: 344.1116). Further elution gave the recovered starting material (20 mg, 15% recovery).

6-(Hydroxymethyl)-3,3-ethylenedioxybicyclo[3.2.1]octane (41)

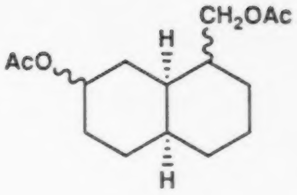


To a suspension of Ra-Ni (0.8 mL, settled volume) in benzene (2 mL) at 5°C under an argon atmosphere, was added compound **40** (103 mg, 0.314 mmol) in benzene (2 mL). The mixture was stirred at room temperature for 4.5 h and filtered. The residue was washed with benzene (2 x 5 mL), benzene and ethanol (1 : 1, 2 x 5 mL) and ethanol (2 x 5 mL). The filtrate and the washing solutions were combined and concentrated to afford the crude product which was purified by flash chromatography. Elution with ether, hexane and ethanol (10:85:5) gave alcohol **41** (ca. 9:1 mixture of two diastereomers, 42 mg, 71% yield) as a colorless oil: ir ($CHCl_3$ cast) 3360 cm^{-1} (br, OH); ^1H nmr (300 MHz) δ 3.88-4.02 (m, 4 H, -OC**H**$_2$C**H**$_2$O-), 3.81 (m, 2 H, -C**H**$_2$OH), 2.28 (m 2 H), 2.16 (m, 1 H), 2.01 (br d, *J* = 14 Hz, 1 H), 1.73-1.85 (m, 4 H), 1.60-1.69 (m, 3 H) and 1.50 (br d, *J* = 11 Hz, 1 H); hrms M^+ 198.1253 (calcd. for $C_{11}H_{18}O_3$: 198.1256). Anal. calcd. for $C_{11}H_{18}O_3$: C 66.64, H 9.15; found: C 66.63, H 9.22.

(1S*, 6S*)-3-Hydroxy-6-(hydroxymethyl)bicyclo[4.4.0]decane (42) and its diacetate (43)



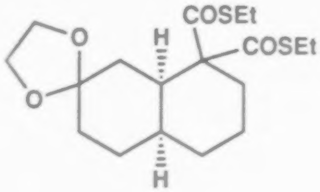
42



43

To a suspension of W-2 Ra-Ni (2 mL, settled volume) in benzene (8 mL), was added compound **32** (183 mg, 0.557 mmol) in benzene (3 mL). The mixture was stirred at room temperature under an argon atmosphere for 5 h and filtered. The residue was washed thoroughly with benzene (2 x 10 mL), benzene and ethanol (1:1, 2 x 10 mL) and ethanol (2 x 10 mL). The filtrate and the washing solutions were combined and concentrated to afford the crude diol **42** (73 mg, 71% yield); ir ($CHCl_3$ cast) 3320-3360 cm^{-1} (OH). To a solution of the crude diol in pyridine (2 mL), was added acetic anhydride (1 mL). The mixture was kept at room temperature in dark overnight. The volatiles were removed by a Kugelrohr distillation apparatus and the residue was subjected to flash chromatography. Elution with ethyl acetate and hexane (15:85) afforded diacetate **43** (93 mg): ir ($CHCl_3$ cast) 1732 cm^{-1} (C=O, acetates); ^1H nmr (400 MHz) δ 4.62-5.02 (4 m, 1 H), 3.78-4.10 (m, 1 H), 3.78-3.87 (m, 1 H), 1.96-2.00 (8 s, 6 H, 2 x $C\mathbf{H}_3COO$-) and 1.18-1.86 (m, 15 H); hrms m/z 225.1487 (M^+-CH_3CO, calcd. for $C_{13}H_{21}O_3$: 225.1491) and 148.1253 (M^+-2 x CH_3COOH, calcd. for $C_{11}H_{16}$: 148.1252).

(1R*,6S*)-10,10-Bis(ethylthiocarbonyl)-3,3-ethylenedioxy-bicyclo[4.4.0]decane (44)



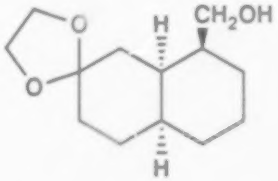
A. Transacetalization

A solution of compound **32** (70 mg, 0.213 mmol), 2-ethyl-2-methyl-1,3-dioxolane (0.74 mL) and *p*-TsOH (4.1 mg, 0.022 mmol) in benzene (5 mL) was heated under reflux for 28 h under an atmosphere of argon. The mixture was then cooled down to room temperature and diluted with benzene (15 mL). The resulting solution was washed with water (5 mL), saturated sodium bicarbonate (5 mL) and brine (5 mL). Filtration and concentration afforded the crude product which was subjected to chromatography. Elution with ethyl acetate and hexane (10:90) gave acetal **44** (79 mg, 100% yield) as a colorless oil: ir ($CHCl_3$ cast) 1698 and 1666 cm^{-1} (C=O, thiolesters); ^1H nmr (300 MHz) δ 3.90 (m, 4 H, -OC**H**$_2$C**H**$_2$O-), 3.04 (ddd, J = 13, 3, 3 Hz, 1 H), 2.81-2.98 (m, 4 H, 2 x -SC**H**$_2$CH$_3$), 2.34 (dm, J = 14, 1 H), 1.48-1.98 (m, 10 H), 1.38 (m, 2H), 1.24 (t, J = 7 Hz, 3 H, -SCH$_2$C**H**$_3$) and 1.22 (t, J = 7 Hz, 3 H, -SCH$_2$C**H**$_3$); hrms M$^+$ 372.1430 (calcd. for $C_{18}H_{28}O_4S_2$: 372.1430).

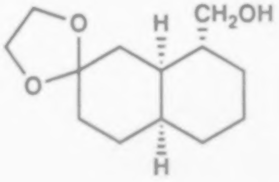
B. Acetalization using ethylene glycol

To a flame dried 50 mL round bottom flask equipped with a 10 mL Dean-Stark water separator connected to a condenser, was charged with a solution of ketone **32** (107 mg, 0.32 mmol), ethlylene glycol (204 mg, 3.3 mmol) and *p*-TsOH (8 mg, 0.04 mmol) in benzene (30 mL). The mixture was heated to reflux under an argon atmosphere for 16 h with azeotropic removal of water. The resulting solution was workeded up and purified as in the preceeding experiment to afford the acetal **44** (91 mg, 75% yield) and recovered starting material (17 mg, 16% recovery).

(1R*,6S*,10S*)-3,3-Ethylenedioxy-10-(hydroxymethyl)-bicyclo[4.4.0]decane (45) and (1R*,6S*,10R*)-3,3-ethylenedioxy-10-(hydroxymethyl)bicyclo[4.4.0]decane (46)



45

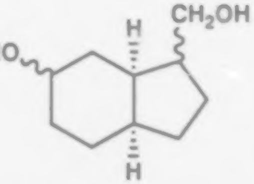


46

To a suspension of W-2 Ra-Ni (1.2 mL, settled volume) in benzene (5 mL), was added acetal **44** (133 mg, 0.363 mmol) in benzene (3 mL). The mixture was stirred at room temperature under argon for 1 h and filtered. The residue was washed thoroughly with benzene (2 x 5 mL), benzene and ethanol (1:1, 2 x 5 mL), and ethanol (2 x 5 mL). Evaporation of the solvent afforded the crude product which was subjected to flash chromatography. Elution with ethyl acetate, hexane and ethanol (10:85:5) gave alcohol **45** (34 mg, 42% yield) as a colorless oil: ir ($CHCl_3$ cast) 3440 cm^{-1} (br, OH); ^1H nmr (300 MHz) δ 3.94 (m, 4 H, -OC**H**$_2$C**H**$_2$O-), 3.62 (m, 2 H, -C**H**$_2$OH), 2.03 (dd, J = 13.5, 7 Hz, 1 H) and 1.30-1.87 (m, 15 H); hrms M^+ 226.1567 (calcd. for $C_{13}H_{22}O_3$: 226.1569). Anal. calcd. for $C_{13}H_{22}O_3$: C 68.99, H 9.80; found: C 68.65, H 9.66.

Further elution afforded alcohol **46** (31 mg, 38% yield): ir ($CHCl_3$ cast) 3420 cm^{-1} (br, OH); ^1H nmr (300 MHz) δ 3.94 (m, 4 H, -OC**H**$_2$C**H**$_2$O-), 3.51 (dd, J = 10.5, 7.5 Hz, 1 H, -C**H**HOH), 3.42 (dd, J= 10.5, 7 Hz, 1 H, -CH**H**OH), 2.14 (ddd, J = 14, 7.5, 3.5 Hz, 1 H), 1.21-1.85 (m, 14 H) and 1.03 (ddd, J = 15, 13, 3.5 Hz, 1 H); hrms M^+ 226.1565 (calcd. for $C_{13}H_{22}O_3$: 226.1569). Anal. calcd. for $C_{13}H_{22}O_3$: C 68.99, H 9.80; found: C 68.92, H 9.80.

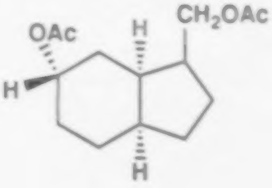
(1R*,6R*)-3-Hydroxy-9-(hydroxymethyl)bicyclo[4.3.0]nonane (47)



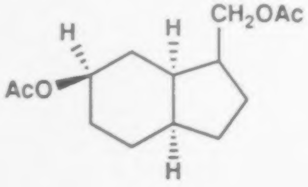
To a suspension of Ra-Ni (1.5 mL, settled volume) in benzene (7 mL), was added compound **34** (128.4 mg, 0.409 mmol) in benzene (3 mL) under an argon atmosphere. The mixture was stirred at room temperature for 3 h and filtered. The residue was washed thoroughly with benzene (2 x 10 mL), benzene and ethanol (1:1, 2 x

10 mL) and ethanol (2 x 10 mL). The solutions were combined and concentrated to afford the crude product which was subjected to flash chromatography. Elution with ethyl acetate and petroleum ether (60:40) gave diol **47** (48 mg, 70% yield) as a colorless oil: ir ($CHCl_3$ cast) 3329 cm^{-1} (br, OH); ^1H nmr (400 MHz) (mixture of diastereomers) δ 4.08 (m), 3.34-3.90 (m), 2.24 (m) and 1.10-2.10 (m); hrms m/z 170.1305 (M^+, calcd. for $C_{10}H_{18}O_2$: 170.1307), 152.1203 (M^+-H_2O, calcd. for $C_{10}H_{16}O$: 152.1201), 134.1097 (M^+-$2H_2O$, calcd. for $C_{10}H_{14}$: 134.1095).

Diacetates 48 and 49



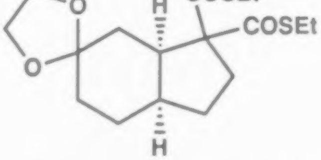
48



49

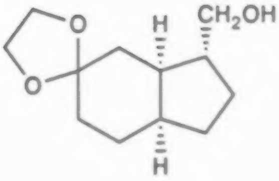
A mixture of diol **47** (40 mg, 0.235 mmol), acetic anhydride (0.2 mL) and pyridine (1 mL) was kept in dark at room temperature for 24 h. The volatiles were removed by vacuum distillation using a Kugelrohr appratus and the residue was subjected to chromatography. Elution with ethyl acetate and petroleum ether (30:70) afforded a mixture of acetates **48** and **49** (59 mg, 100% yield) as a colorless oil: ir ($CHCl_3$ cast) 1738 cm^{-1} (C=O, acetates); ^1H nmr (300 MHz) (two diastereomers, 9:1 ratio) δ 5.06 (m, 1 H) and 4.00 (m, 2 H) for the minor; δ 4.67 (tt, J = 11.5, 3.5 Hz, 1 H), 4.07 (dd, J = 11, 6.7 Hz, 1 H) and 3.91 (dd, J = 11, 9 Hz, 1 H) for the major; the rest of the protons appeared at δ 1.10-2.35; hrms m/z 152.1201 (M^+ - CH_3COOH - CH_3CO, calcd. for $C_{10}H_{16}O$: 152.1201), 134.1099 (M^+ - 2 x CH_3COOH, calcd. for $C_{10}H_{14}$: 134.1095).

(1R*,6S*)-9,9-Bis(ethylthiocarbonyl)-3,3-ethylenedioxybicyclo[4.3.0]nonane (50)

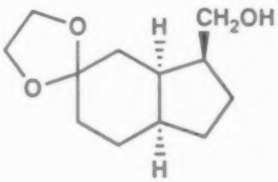


Employing the same procedures discribed prevously for the transacetalization and acetalization of ketone **32**, ketone **34** was converted to acetal **50** in quantitative yield: ir ($CHCl_3$ cast) 1688 and 1664 cm^{-1} (thiolesters); ^1H nmr (300 MHz) δ 3.94 (m, 4 H, -$OC\mathbf{H}_2C\mathbf{H}_2O$-), 3.07 (ddd, *J* = 13, 5, 5 Hz, 1 H), 2.83-2.95 (m, 4 H, 2 x -$SC\mathbf{H}_2CH_3$), 2.44-2.62 (m, 2 H), 2.10 (m, 1 H), 1.86 (m, 1 H), 1.50-1.77 (m, 7 H), 1.25 (t, *J* = 7 Hz, 3 H, -$SCH_2C\mathbf{H}_3$) and 1.23 (t, *J* = 7 Hz, 3 H, -$SCH_2C\mathbf{H}_3$); hrms M^+ 358.1266 (calcd. for $C_{17}H_{26}O_4S_2$: 358.1272).

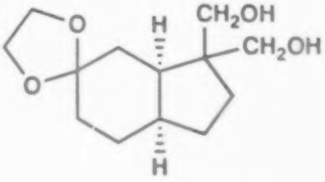
(1R*,6S*,9R*)-3,3-Ethylenedioxy-9-(hydroxymethyl)-bicyclo[4.3.0]nonane (51), (1R*,6S*,9S*)-3,3-ethylenedioxy-9-(hydroxymethyl)bicyclo[4.3.0]nonane (52) and (1R*,6S*)-3,3-ethylenedioxy-9,9-di(hydroxymethyl)bicyclo[4.3.0]nonane (53)



51



52



53

To a suspension of Ra-Ni (2.5 mL, settled volume) in benzene (5 mL) under an argon atmosphere, was added compound **50** (194 mg, 0.542 mmol) in benzene (5 mL). The mixture was stirred at room temperature for 3 h and filtered. The residue was washed thoroughly with benzene (2 x 10 mL), benzene and ethanol (1:1, 2 x 10 mL) and ethanol (2 x 10 mL). After concentration, the crude product (112 mg) was subjected to flash chromatography. Elution with ethyl acetate, hexane and ethanol (20:75:5) afforded alcohol **51** (6 mg, 5% yield) as a colorless oil: ir ($CHCl_3$ cast) 3412 cm^{-1} (br, OH); ^{1}H nmr (300 MHz) δ 3.94 (m, 4 H, -OC**H**$_2$C**H**$_2$O-), 3.34 (s, 1 H, -O**H**), 3.45-3.70 (m, 2 H, -C**H**$_2$OH), 2.50 (m, 1 H) and 1.25-2.35 (m, 12 H); hrms m/z 212.1417 (M$^+$, calcd. for $C_{12}H_{20}O_3$: 212.1412), 194.1304 (M$^+$ - H_2O, calcd. for $C_{12}H_{18}O_2$: 194.1307).

Further elution gave a mixture of **51** and **52** (3.6:1, 65 mg, 57% yield) and pure **51** (9 mg, 8% yield), each as a colorless oil. Compound **52** showed the following spectral data: ir ($CHCl_3$ cast) 3408 cm^{-1} (br, OH); ^{1}H nmr (300 MHz) δ 3.94 (m, 4 H, -OC**H**$_2$C**H**$_2$O-), 3.73 (s, 1 H, -O**H**), 3.50-3.60 (m, 2 H, -C**H**$_2$OH), 2.45 (m,1H) and 1.20-2.30 (m, 12 H); hrms 212.1413 (M$^+$, calcd. for

$C_{12}H_{20}O_3$: 212.1412), 194.1308(M^+ - H_2O, calcd. for $C_{12}H_{18}O_2$: 194.1307) .

Continued elution gave diol **53** (30 mg, 23% yield) as a white solid: m.p. 169-170°C; ir (nujol) 3250 cm^{-1} (br, OH); ^1H nmr (300 MHz, DMSO-d_6) δ 4.46 (t, *J* = 5 Hz, 1 H, -O**H**), 4.30 (t, *J* = 4.5 Hz, 1 H, -O**H**), 3.82 (m, 4 H, -OC**H**$_2$C**H**$_2$O-), 3.20-3.38 (m, 5 H), 2.10 (m, 1 H), 1.88 (dt, *J* = 13, 5 Hz, 1 H) and 1.16-1.79 (m, 9 H); cims $[M + NH_4]^+$ 260, $[M + H]^+$ 243 and M^+ 242.

References

(1) Muhler *Ann.* **1875**, *176*, 181.

(2) Ralston, A. W.; Segebrecht, E. W.; Bauer, S. T. *J. Org. Chem.* **1939**, *4*, 502.

(3) Field, L. *Synthesis* **1972**, 101.

(4) Bruice, T. C. in *Organic Sulfur Compounds*; Kharasch, N., Ed.; Pergamon Press: Oxford, 1961.

(5) Barrett, G. C. in *Organic Compounds of Sulfur, Selenium, and Tellurium*; Specialist Periodical Reports, Vol. 4, Burlington House: London, 1977; P 14.

(6) Hausler, J.; Schmidt, U. *Chem. Ber.* **1974**, *107*, 2804.

(7) Warwell, S.; Ahfaenger, B. *Chemikerztg.* **1977**, *101*, 103.

(8) Masamune, S.; Kamata, S.; Diakur, J.; Sugihara, Y.; Bates, G. S. *Can. J. Chem.* **1975**, *53*, 3693.

(9) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 5829.

(10) Watanabe, Y.; Shoda, S.-I.; Mukayama, T. *Chem. Lett.* **1976**, 741.

(11) Hepworth, H.; Clapham, H. W. *J. Chem. Soc.* **1921**, *119*, 1188.

(12) Rimpler, M. *Chem. Ber.* **1966**, *99*, 1528.

(13) Cahours, A. *Bull. Soc. Chim. France* **1876**, *25*, 563.

(14) Gustus, E. L.; Stevens, P. G. *J. Am. Chem. Soc.* **1933**, *55*, 378 .

(15) Grieco, P. A.; Yokoyama, Y.; Williams, E. *J. Org. Chem.* **1978**, *43*, 1283.

(16) Reid, E. E. in *Organic Chemistry of Bivalent Sulphur Compounds*; Chemical Publishing Company: New York, 1962.

(17) Weygang, F.; Steglich, W. *Chem. Ber.* **1960**, *93*, 2983.

(18) Grunwell, J. R.; Foerst, D. L. *Synth. Commun.* **1976**, *6*, 453.

(19) Liu, H. J.; Sabesan, S. I. *Can. J. Chem.* **1980**, *58*, 2645.

(20) Horik, K. *Synth. Commun.* **1977**, *7*, 251.

(21) Nair, P. G.; Joshua, C. P. *Indian J. Chem.* **1975**, *13*, 35.

(22) Imamoto, T.; Kodera, M.; Yokoyama, M. *Synthesis* **1982**, 134.

(23) Yamada, S.; Yokoyama, Y.; Shioiri, T. *J. Org. Chem.* **1974**, *39*, 3302.

(24) Liu, H. J.; Lee, S. P.; Chan, W. H. *Synth. Commun.* **1979**, *9*, 91.

(25) Arrieta, A.; Garcia, T.; Lago, T. M.; Palomo, C. *Synth. Commun.* **1983**, *13*, 471.

(26) Sekine, M.; Kume, A.; Hata, T. *Tetrahedron Lett.* **1981**, 3617.

(27) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683.

(28) Back, T. G. *Tetrahedron* **1977**, *33*, 3041.

(29) Corey, E. J.; Nicolaou, N. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614.

(30) Corey, E. J.; Brunelle, D. J.; Stork, P. J. *Tetrahedron Lett.* **1976**, 3045.

(31) Gerlach, H.; Thalmann, A. *Helv. Chim. Acta* **1974**, *57*, 293.

(32) Gerlach, H.; Oertle, K.; Thalmann, A.; Servi, S. *Helv. Chim. Acta* **1975**, *58*, 2036.

(33) Masamune, S.; Yamamoto, H.; Kamata, S.; Fukuzawa, A. *J. Am. Chem. Soc.* **1975**, *97*, 3513.

(34) Gerlach, H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta* **1976**, *59*, 755.

(35) Gerlach, H.; Kuenzler, R. *Helv. Chim. Acta* **1978**, *61*, 2503.

(36) Nagao, Y.; Kawabata, K.; Fijita, E. *J. Chem. Soc., Chem. Commun.* **1978**, 330.

(37) Liu, H. J.; Bukownik, R. R.; Pednekar, P. R. *Synth. Commun.* **1981**, *11*, 599.

(38) Liu, H. J.; Wynn, H. *Can. J. Chem.* **1986**, *64*, 649.

(39) Jeger, O.; Norymberski, J.; Szipilfogel, S.; Prelog, V. *Heiv. Chim. Acta* **1946**, *29*, 360.

(40) Prelog, V.; Norymberski, J.; Jeger, O. *Helv. Chim. Acta* **1946**, *29*, 684.

(41) Wolfrom, M. L.; Karabinos, J. V. *J. Am. Chem. Soc.* **1946**, *68*, 1455.

(42) Mclintosh, A. V. J.; Meinzer, E. M.; Levin, R. H. *J. Am. Chem. Soc.* **1948**, *70*, 2955.

(43) Mclintosh, A. V. J.; Searcy, A. M.; Meinzer, E. M.; Levin, R. H. *J. Am. Chem. Soc.* **1949**, *71*, 3317.

(44) Liu, H. J.; Lai, H. K. *Tetrahedron Lett.* **1979**, 1193.

(45) Liu, H. J.; Lai, H. K. *Can. J. Chem.* **1979**, *57*, 2522.

(46) Purvis, J. E.; Jones, H. O.; Tasker, H. S. *J. Chem. Soc.* **1910**, *97*, 2289.

(47) Scheithauer, S.; Mayer, R. *Chem. Ber.* **1967**, *100*, 1413.

(48) Imamoto, T.; Kodera, M.; Yokoyama, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2303.

(49) Oppong, I. V. Ph.D Thesis, the University of Alberta, Edmonton, Alberta, Canada, 1984; P. 39.

(50) Liu, H. J.; Oppong, I. V. *Can. J. Chem.* **1982**, *60*, 94.

(51) van Tamelen, E. E.; Hildahl, G. T. *J. Am. Chem. Soc.* **1956**, *78*, 4405.

(52) Chapman, O. L.; Fitton, P. *J. Am. Chem. Soc.* **1963**, *85*, 41.

(53) Biffin, M. E. C.; Moritz, A. G.; Paul, D. B. *Aust. J. Chem.* **1972**, *25*, 1329.

(54) Finkelstein, H. *Ber.* **1910**, *43*, 1528.

(55) Fedorynski, M.; Wojciechowski, K.; Matacz, Z.; Makosa, M. *J. Org. Chem.* **1978**, *43*, 4682.

(56) Lavallee, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* **1988**, *29*, 6033.

(57) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015.

(58) Kircher, H. W.; Rosenstein, F. U. *J. Org. Chem.* **1987**, *52*, 2586.

(59) Grieco, P. A.; Nishizawa, N.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102.

(60) Stork, G.; Danheiser, R. *J. Org. Chem.* **1973**, *38*, 1775.

(61) Kieczykowski, G. R.; Quesada, M. L.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 782.

(62) Guaciaro, M. A.; Wovkulich, P. M; Smith, A. B. III *Tetrahedron Lett.* **1978**, 4661.

(63) Shih, C.; Fritzen, E. C.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 4462.

(64) Baldwin, J. E.; Adlington, R. M.; Robertson, J. *Tetrahedron* **1989**, *45*, 909.

(65) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*; John Wiley & Sons, Inc.: New York, 1981.

(66) Rabenstein, D. R.; Nakashima, T. T. *Anal. Chem.* **1979**, *51*, 1465A.

(67) Patt, S. K.; Shoolery, T. N. *J. Magn. Res.* **1982**, *46*, 535.

(68) Still, C. W.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

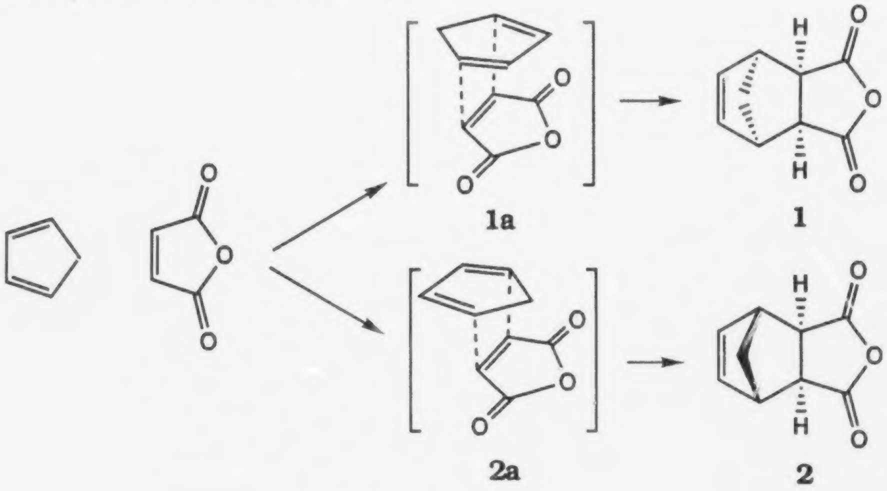
CHAPTER II

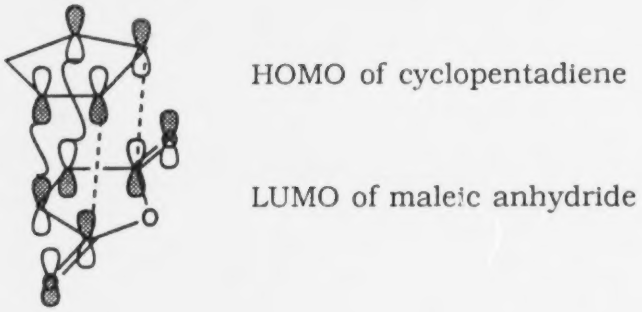
FACIAL SELECTIVITY IN DIELS-ALDER REACTION OF 4,4-DISUBSTITUTED 2,5-CYCLOHEXADIENONES

Introduction

Since its formulation in 1928,[1] the Diels-Alder reaction has been refined to become one of the most powerful tools in organic synthesis.[2-5] For example, it has been used as key steps to construct a variety of natural products such as steroids,[6,7] alkaloids[8,9] and prostaglandins.[10] At the same time, the detailed mechanism of this reaction, even in the simplest case of reaction between butadiene and ethylene, is still somewhat controversial. While it is now generally accepted that most Diels-Alder reactions are concerted with respect to the retention of stereochemistry during reactions, it is not clear whether all or indeed any are synchronous. Woodward-Hoffmann's Orbital Symmetry Conservation theory[11] predicts that the suprafacial approach $[\pi_{4S} + \pi_{2S}]$ of diene and dienophile is symmetry allowed and consequently can be a synchronous reaction. Also Houk and coworkers[12] reported that the reaction of butadiene with ethylene is consistent with a synchronous or nearly synchronous concerted mechanism. On the other hand, calculations according to MINDO/3[13,14] contradict these results in favor of an unsymmetrical transition state and a biradical-like intermediate.

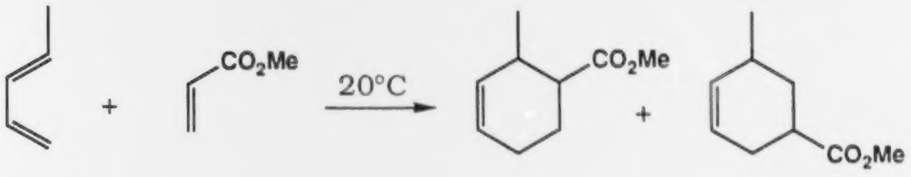
The early development of a series of empirical rules by Alder and Stein[15] for predicting the structural outcome of Diels-Alder reactions greatly facilitated its use in organic synthesis. The *cis* principle predicts that additions to the diene in the required cisoid conformation occurs from the same side at each end of the diene moiety and also that attack at both ends of the dienophilic double bond occurs from the same face of dienophile. It further predicts that the relative configuration of the substituents in the transition state is preserved in the product. The *endo* rule, originally formulated for cyclic dienes with dienophiles,[15,16] predicts that the more favored addition product is the one obtained from a transition state with the "maximum accumulation of double bonds".[1] In principle, the reaction between cyclopentadiene and maleic anhydride may proceed through two "sandwich-like" transition states, **1a** and **2a**. The one with the "maximum accumulation of double bonds" is the *endo* transition state **1a**. In the actual reaction, the exclusive product was *endo*-adduct **1**[17] rather than **2**. This effect has been rationalized[11] by a stabilization of the *endo* transition state by secondary orbital interaction (as shown by the dashed line in **3**).





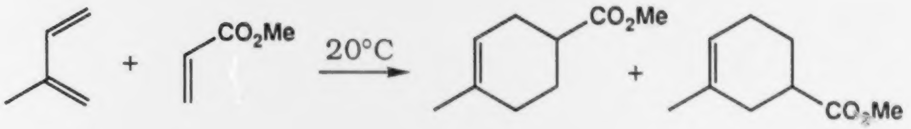
3

Diels-Alder addition of unsymmetrical dienes and dienophiles show a strong preference for the formation of specific regioisomers.[18-20] The regiochemistry of Diels-Alder cycloadditions between unsymmetrical dienes and dienophiles can be predicted by using a set of orientational rules. In the reaction of electron-rich dienes and electron-deficient dienophiles, 1-substituted dienes preferentially give the "*ortho*" isomer in which the C_1 substituent from the diene constituent is adjacent (*ortho*) to the substituent from the dienophile. On the other hand, 2-substituted dienes give mainly the "*para*" isomer. Thus the reaction of *trans*-piperylene with methyl acrylate afforded adduct **4**[16] as the principle product rather than adduct **5**. While the reaction of isoprene with methyl acrylate gave adduct **6**[16] as the major product. The reasons for these orientational effects have long been puzzling. Most investigators[21-24] have used the Frontier Molecular Orbital (FMO) approach in which the regiochemistry is predicted from the primary interactions of frontier molecular orbitals. Using the same approach, Houk[25] predicted that when both the diene and dienophile are electron rich, the "*meta*" orientation will be favored. This has since been observed experimentally by Fleming *et al.*[26]



4 **5** (18 : 1)

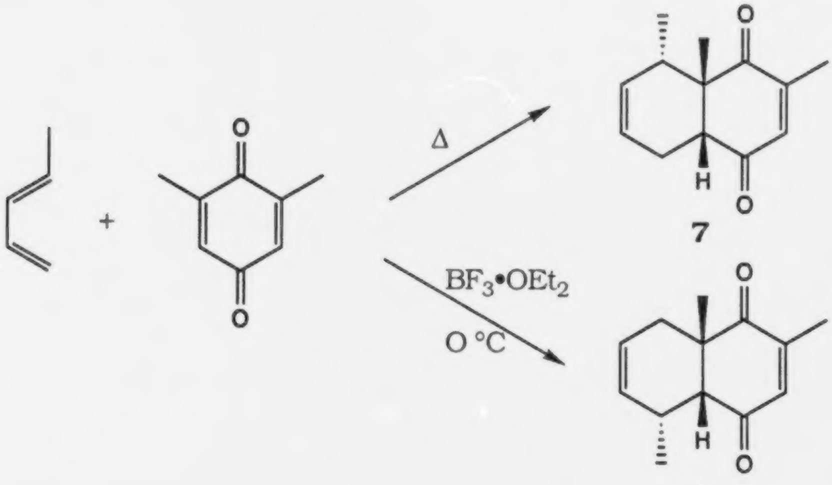
"ortho" *"meta"*



6 (5.4 : 1)

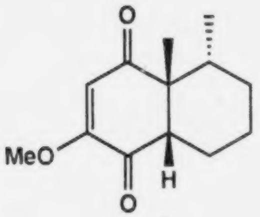
"para" *"meta"*

It has been found that Lewis acids such as aluminum chloride, boron trifluoride and stannic chloride produce large increases in the rate of Diels-Alder reactions.[27] For example, butadiene and methyl vinyl ketone reacted in one hour at room temperature in the presence of stannic chloride to give a 73% yield of acetylcyclohexene. In the absence of a catalyst however no adduct was formed. Furthermore, catalysis by Lewis acids can also influence the regio- and stereochemistry of Diels-Alder reactions so that the *ortho*-[28-30] and *para*-selectivity[31-33] of the addition as well as the *endo*-selectivity[34-37] are greatly enhanced. On the other hand, Valenta and coworkers[38] reported a reversal of regioselectivity of Diels-Alder reactions of quinones catalyzed by Lewis acids. Thus, the thermal reaction of 2,6-dimethylquinone with *trans*-piperylene afforded **7** while the boron trifluoride catalyzed reaction gave **8**. It had been previously assumed that in a Diels-Alder reaction, the Lewis acids which enhance regioselectivity would increase the formation of the same regioisomer. It now appears that this is not the case and the orientation of the product may depend on the Lewis acid used.[39] Thus the reaction of 2-methoxy-5-methylbenzoquinone with *trans*-piperylene at -16 °C using stannic chloride as a catalyst, gave a 1:20 mixture of adducts **9** and **10**. On the contrary, the same reaction catalyzed by boron trifluoride afforded a 4:1 mixture of adducts **9** and **10**.

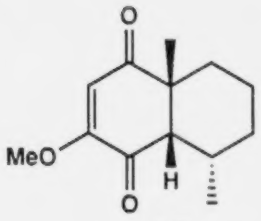


7

8

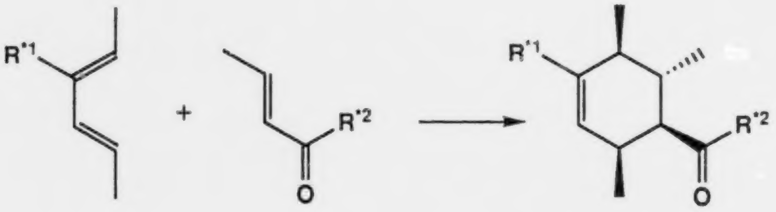


9



10

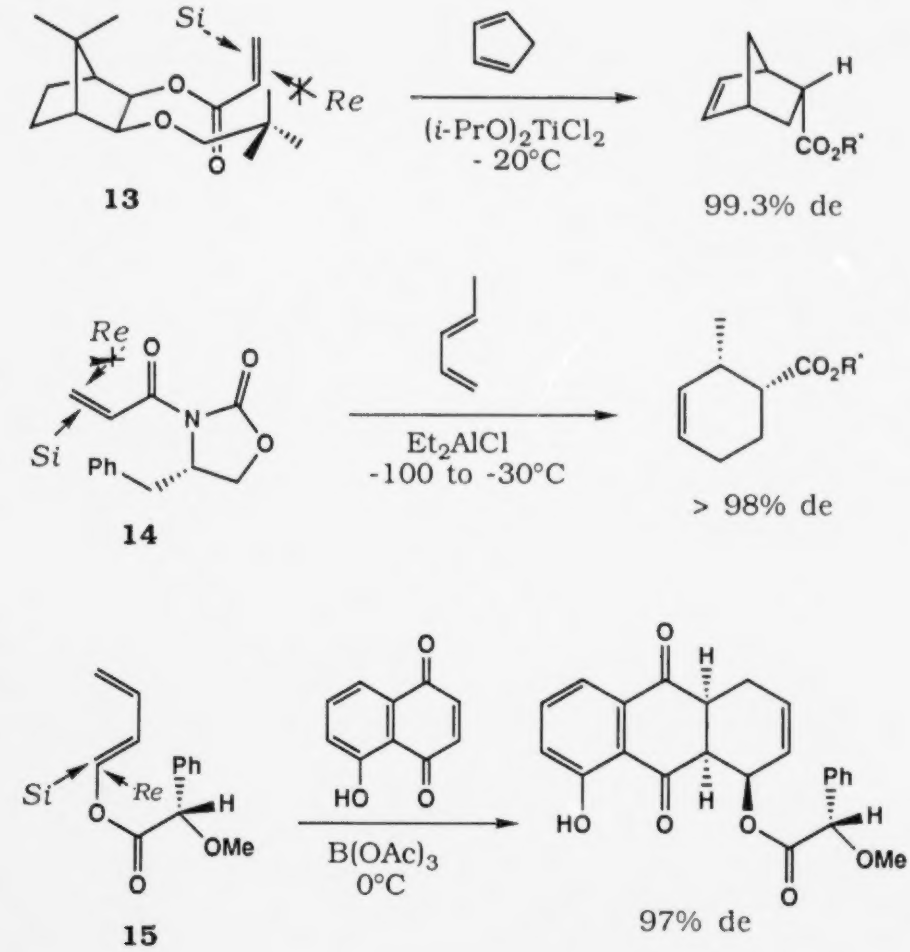
One of the most attractive features of the Diels-Alder reaction is its capability of generating four contiguous stereogenic centers in one synthetic operation. As discussed previously, the regio- and stereochemistry (*endo vs exo*) may be controlled by favorable orbital interactions. There is another stereochemical feature, the π-facial diastereoselectivity which arises when the addends possess two different reactive faces, that has attracted considerable attention in recent years. The asymmetric Diels-Alder reaction[40,41] pioneered by Wolborsky,[42,43] for example, has been established as one of the most important tools in modern asymmetric synthesis. As illustrated in Equation 1, the reaction of two chiral components, diene **11** and dienophile **12**, can hypothetically produce $2^4 = 16$ stereoisomers. However, potential stereoselection could be attained with the aid of the elements which govern the stereochemical course of the reaction, such as *cis*-addition, *endo*-addition and diastereofacial selectivities (orientation of diene and dienophile in the transition state). Most of the asymmetric Diels-Alder reactions involve optically active dienophiles[44-52] or dienes[53-55] which carry a removable chiral auxiliary group. As illustrated in Scheme 1, compounds **13-15** undergo Diels-Alder reactions in the presence of Lewis acid catalyst with excellent diastereoselectivity. They were devised in such a way that the chiral auxiliary group effectively blocked the *Re* face of the dienophile or diene and therefore this induced high diastereoselectivities. An elegant study by Masamune and coworkers[56] demonstrated the importance of rational design when both chiral diene and dienophile are involved (Scheme 2). The reaction of the matched pair of chiral diene **16** and dienophile **17** gave adducts **18** and **19** in a ratio of 40:1. While the mismatched pair **16** and **20** afforded adducts **21** and **22** in a 1:2 ratio. In the matched pair, the diastereofacial selectivities of both reactants in forming **18** are acting in concert, resulting in high selectivity. In the mismatched pair however the diastereoselectivities of **16** and **20** are counteracting each other, and as a result, poor selectivity was observed.



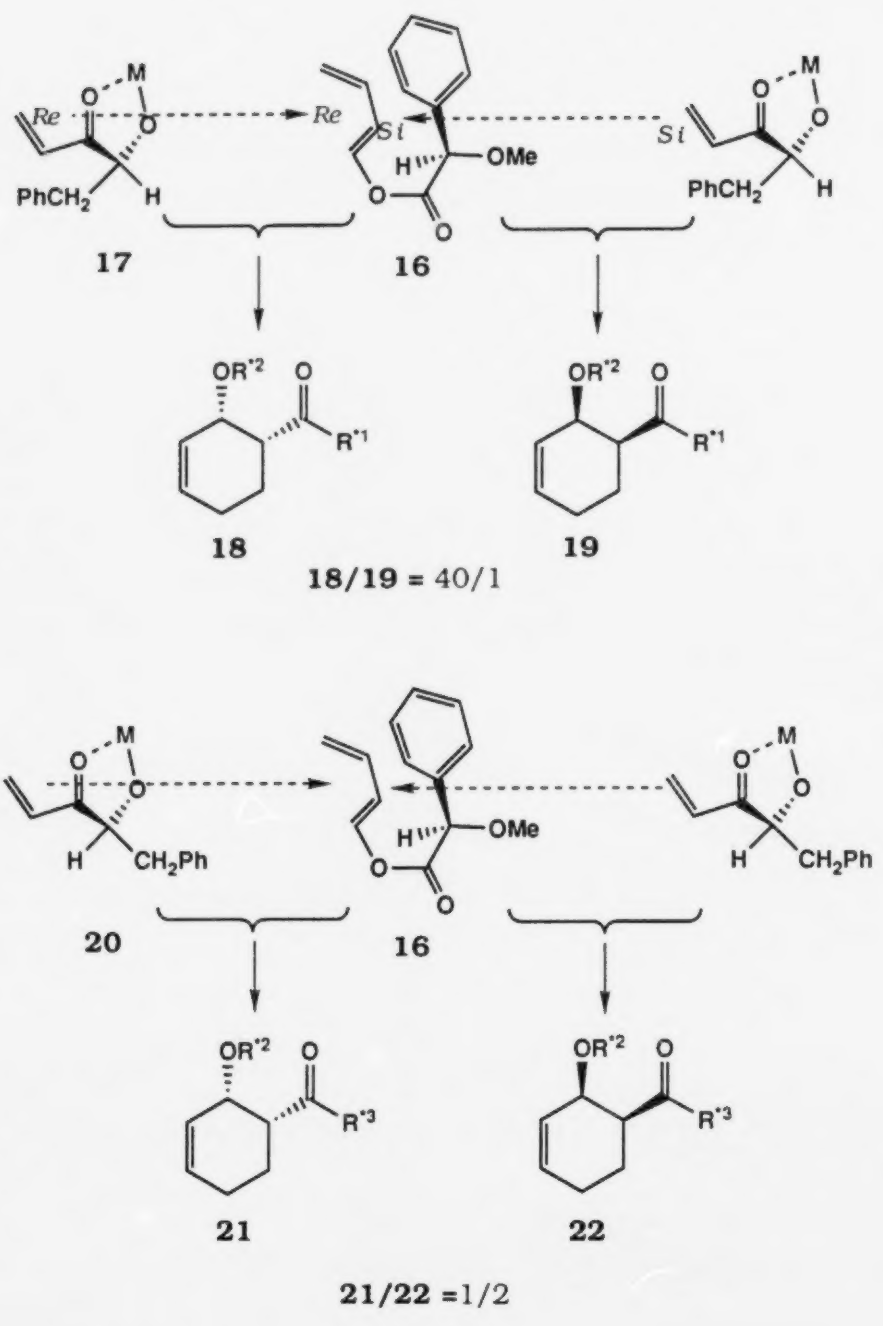
11 **12**

(Eq. 1)

Compared to the use of a covalently attached chiral auxiliary group, the use of a chiral catalyst appears to be a potentially more attractive method to induce asymmetric Diels-Alder reactions of prochiral dienes and dienophiles as two synthetic steps could be avoided. However, studies using Lewis acids such as menthoxyaluminium dichloride,[57] cyclohexanol derivatives of alkoxyaluminium dichloride,[58] Eu(hfc)$_3$,[59] acyloxyborane[60] and alkoxytitanium(IV) reagents[61,62] gave variable results. Among them only the chiral titanium reagents furnished asymmetric induction greater than 90%.


Si
Re
13
(i-PrO)$_2$TiCl$_2$
- 20°C
H
CO$_2$R*
99.3% de
Re
Si
Ph
14
Et$_2$AlCl
-100 to -30°C
CO$_2$R*
> 98% de
Si
Re
Ph
H
OMe
15
HO
B(OAc)$_3$
0°C
H
HO
Ph
H
OMe
97% de

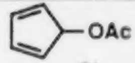
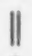
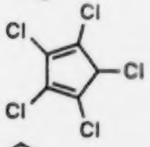
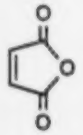
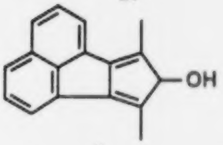
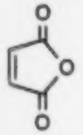
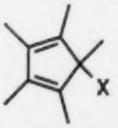
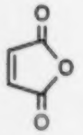
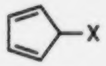
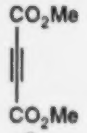
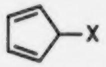
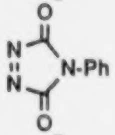
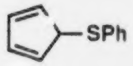
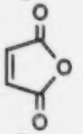
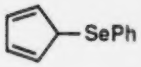
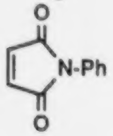
Scheme 1

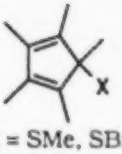
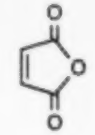
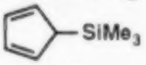
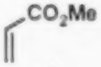
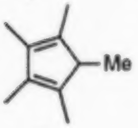
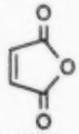
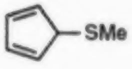
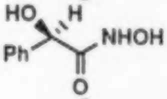
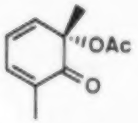
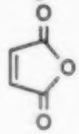
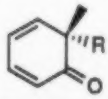
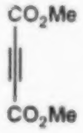
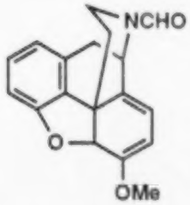
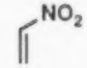
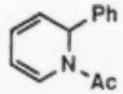
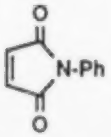
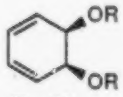
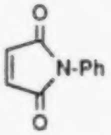

M
O
O
Re
Re
Si
Si
H
OMe
PhCH2
H
O
O
17
16
OR*2
O
R*1
18
19
18/19 = 40/1
M
O
O
H
CH2Ph
OMe
20
16
OR*2
O
R*3
21
22
21/22 =1/2

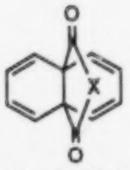
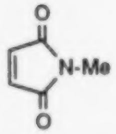
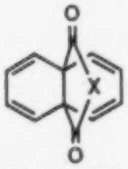
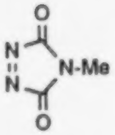
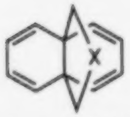
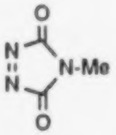
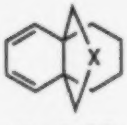
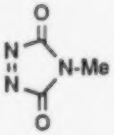
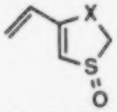
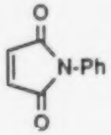
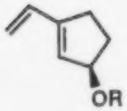
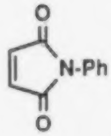
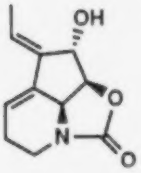
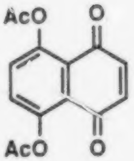
Scheme 2

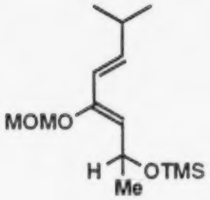
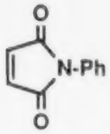
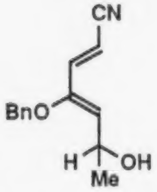
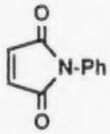
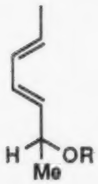
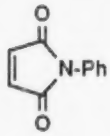
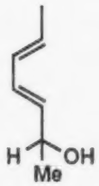
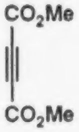
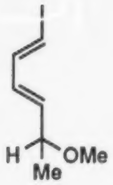
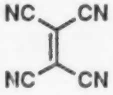
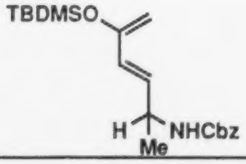
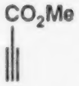
While steric interactions can be invoked to explain the observed facial selectivities in many Diels-Alder cycloadditions,[40,63,64] especially in asymmetrical Diels-Alder reaction, in numerous instances, the π-facial selectivity does not seem to be controlled by steric factors. One of the most studied cases is the facial selectivity concerning 1,3-cyclopentadienes, especially 5-heterosubstituted cyclopentadienes and related compounds (Table 1, entries 1-12).[37,65-75] In many of these cycloadditions, the dienophile reacts preferentially with the more sterically hindered *syn* face (with respect to the electronegative heteroatom) of the cyclic diene. For 5-oxygen, 5-sulfur and 5-selenium substituted cyclopentadienes, the observed facial preferences have been rationalized by Fukui, *et al*[76] and others[77] by orbital mixing between the lone-pair electrons and the diene HOMO. Alternatively, Anh[78] suggested that a beneficial interaction of the antisymmetric oxygen orbital with the diene LUMO is the dominant influence. Recently, Fallis and Macaulay[69] explained the observed facial selectivities on the basis of the Cieplak concept.[79,80] They concluded that on the basis of hyperconjugation and the beneficial interaction with the incipient bond one should expect the cycloaddition of the cyclopentadienes to display a preference for *anti* addition to the antiperiplanar σ bond that was the better donor. Figures 1 and 2 illustrate the favorable interaction of the antiplanar σ bond with the diene HOMO and the developing incipient bonds with the LUMO of the dienophile.

Table 1. π-Facial selectivity of dienes.

entry	diene	dienophile	selectivity (~ratio)	ref
1			syn (10:0)	65
2			syn (9:1)	37, 66, 67
3			syn (10:0)	68
4	 X = Cl, OH, OMe, NHAc		syn (10:0)	69
5	 X = Cl X = Br		anti (1.5:1) anti (10:0)	70
6	 X = Br, I		anti (10:0)	71
7			anti (6:4)	72
8			anti (10:0)	72

9	 X = SMe, SBn X = SPh X = SOMe, SO_2Me		anti (9:1) anti (9.7:0.3) anti (10:0)	69
10			anti (10:0)	73
11			anti (4:1)	74
12		 HO H Ph NHOH O	anti (2.6:1)	75
13			syn (10:0)	81
14	 R = CO_2Me R = CH_2OAc	 CO2Me CO2Me	anti (3:1) anti (0.9:1)	82
15			syn (10:0)	83
16			syn (3:1)	84
17	 R = H R = Ac		syn (16:1) syn (6.5:1)	85

18	 X = O, NMe		anti (10:0)	86
19	 X = O, NMe		syn (10:0)	87, 88
20	 $X = CH_2, O, NH_2, S$ $X = SO_2$		anti (10:0) syn (9.5:0.5)	87, 88
21	 $X = S, SO_2$		syn (10:0)	87, 88
22	 $X = 0, CH_2$		anti (10:0)	89, 90
23	 R = H R = Me,TBDMS		syn (6.4:3.6) anti (10:0)	90
24			anti to OH (9:1)	91

25			syn (10:0)	92
26			syn (10:0)	93
27	 R = H R = Me R = TMS		 syn (1.7:1) syn (5:1) syn (7.3:1)	94
28			anti (2.7:1)	94
29			anti (2:1)	95
30			anti (3:1)	96, 97

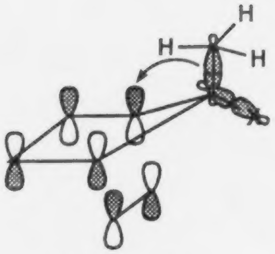


Figure 1

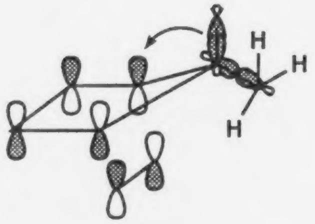
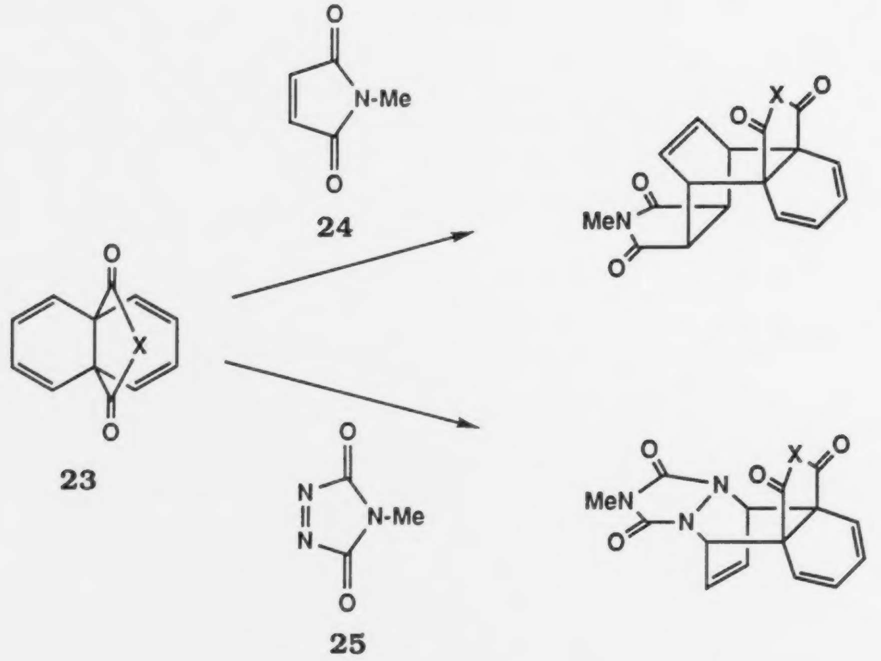


Figure 2

Apart from 1,3-cyclopentadienes, the facial selectivities of 1,3-cyclohexadienes (Table 1, entries 13-21),[81-88] conformationally locked 1(*E*)-substituted 1,3-dienes (Table 1, entries 22-24)[89-91] and allylic substituted acyclic 1,3-dienes (Table 1, entries 25-30)[92-97] have also been extensively studied. On the basis of electrostatic interactions Kahn and Hehre[98] concluded that electrophilic dienophiles should add preferentially to the more nucleophilic diene face, *syn* to "a lone-pair containing allylic substituent". However, this simple model can not be extended in a straightforward manner to sulfur systems (entries 7, 9). The *anti* facial selectivity in the 1(*E*)-substituted 1,3-dienes (Table 1, entries 28-30) was attributed to destabilizing electronic interactions between the heteroatom and the dienophile in the *syn* transition state.[90] One extremely interesting case concerning the facial selectivity of Diels-Alder reactions involves propellanes (Table 1 entries 18-21).[86-88] It was observed that subtle changes can exert a major impact on the course of the cycloaddition. For example, the reactions of the heterocyclic propellanes **23** with N-methyl maleimide (**24**) (Table 1, entry 18) and N-methyltriazolinedione

(**25**) (Table 1, entry 19) showed completely different facial selectivity with regard to the notational heterocyclic bridge in **23**. While the *anti*-stereochemical course can be rationalized in terms of relative steric contributions of the flanking bridge, the same argument is not applicable to the reaction between **23** and **25**. A convincing explanation employing the secondary orbital interaction model has been advanced by Gleiter and Ginsberg.[87,88] As illustrated in Figure 3, the transition state for *syn* attack is stabilized by interactions between the n combinations of the N-N lone pairs of the nitrogen atoms and the antisymmetric π^* orbital of the CO-X-CO bridge, resulting in the exclusive formation of *syn* product.

In studies on the isocyclopentadiene and related compounds[99-104] (e.g., **26**), it was observed that dienophiles reacted preferentially from the bottom face of the diene to give compounds such as **27** (Eq. 2). Paquette and coworkers[105] attributed the observed facial selectivity to the favorable σ/π interactions of the diene and the dienonphile experienced in the transition state, while Houk and Brown[106] attibuted the *endo* attack to torsional and steric effects. Clearly a delicate balance of many different factors influences the facial selectivity of these cycloadditions. Care must be taken in predicting the facial selectivity since one or many factors could be important in any of the cycloadditions.


O
N-Me
O
24
O
X
O
23
O
N
N
N-Me
O
25
O
X
O
O
MeN
O
O
X
O
O
MeN
N
N
O

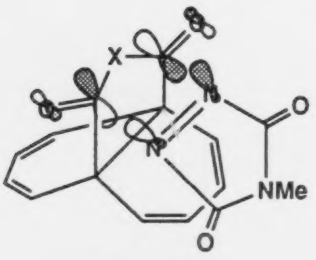
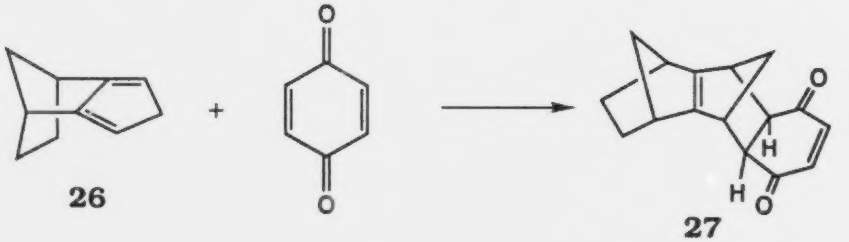
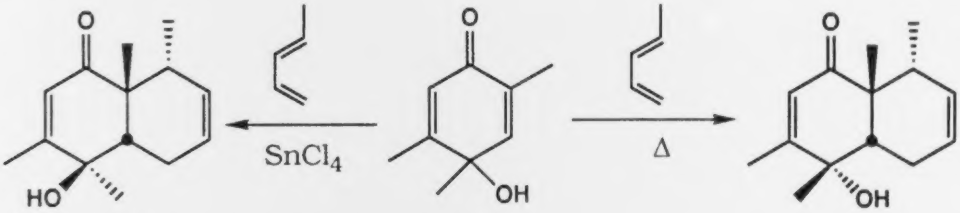

X
O
N
N
O
NMe
O

Figure 3


26
+
O
O
O
H
H
O
27

(Eq. 2)

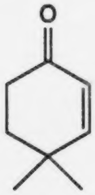
Compared to dienes, limited attention has been focused on the facial selectivity of unsymmetrical dienophiles (excluding chiral dienophiles in asymmetric Diels-Alder reactions).[107-115] Most of these studies have been directed towards natural products synthesis. In virtually all cases, the observed facial selection can be rationalized on the basis of steric interactions. One interesting example involves dienone **28**.[111] When compound **28** was reacted with *trans*-piperylene under thermal conditions, the exclusive product **29** was the one from the hydroxy face. Under Lewis acid ($SnCl_4$) catalysis, the stereochemistry of the adduct **30** was reversed as a result of complexation of the hydroxy group with $SnCl_4$, thereby transforming it into the larger of the geminal substituents (Scheme 3).



30 **28** **29**

Scheme 3

In principle, the addition of substituted cyclohexenones to a substituted 1,3-butadiene is a versatile approach to the decalin system. However, the thermal addition of dienes to cyclohexenones requires drastic conditions and usually produces low yields of the adducts.[116] In recent years, the use of Lewis acid catalysts has led to the utilization of specifically functionalized dienes and dienophiles to produce previously unattainable substitution patterns regio- and stereoselectively. Wenkert and coworkers[117-121] have made an extensive study of the Diels-Alder reaction of cycloalkenones using $AlCl_3$ as a catalyst. Liu and Browne[122-125] have carried out an extensive study of the Diels-Alder additions of 4,4-dimethyl-2-cyclohexenones **31-33**. It was observed that both reaction rate and yield could be improved by the introduction of an additional electron-withdrawing group into the dienophilic moiety as predicted by Alder's rule.[16,126] It was also observed that the regiochemical outcome in the reaction of isoprene with dienone **33** could be affected by different Lewis acids used. Thus the reaction of isoprene with dienone **33**[120] at room temperature using boron trifluoride as catalyst gave adducts **34** and **35** in a ratio of 30:70, while the same reaction catalyzed by stannic chloride produced an 82:18 ratio of adducts **34** and **35**. The formation of the abnormal *anti-para* adduct **35** has been rationalized by a steric effect. Since boron trifluoride can only coordinate with one ligand, it preferentially complexes with the enone carbonyl. As a result, transition state **A** was favored. Since the electron withdrawing effect on the dienophilic double bond promoting *para*-rule guided addition (**34A**) was insufficient to counteract the steric directing effect which promoted *anti-para* addition (**35A**), adduct **35** was predominantly formed rather than **34**. In the case of $SnCl_4$, the Lewis acid was capable of forming a hexacoordinated complex with β-dicarbonyl compounds. In this complex **36** the electron withdrawing effect of the Lewis acid acting through both carbonyls, led to the formation of **34** as the major product via **34B**. This rationalization has been substantiated by the use of dienophile **37**.[127] The Diels-Alder cycloaddition of **37** with isoprene under the catalysis of a variety of Lewis acids gave adduct **38** as the exclusive product. It therefore appears that other than catalyst selection, a remote structural feature such as the cross-conjugated double bond in this dienophile system played an important role in the regio- and stereochemical outcome of the Diels-Alder reaction.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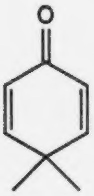
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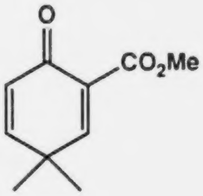
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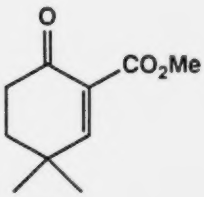
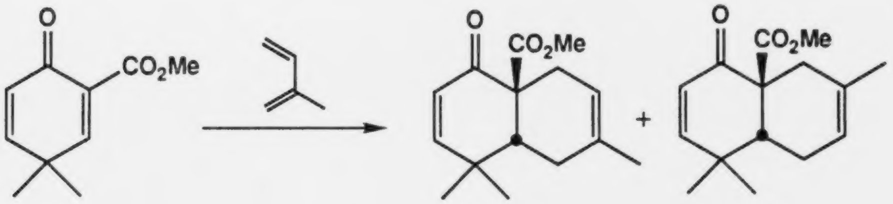
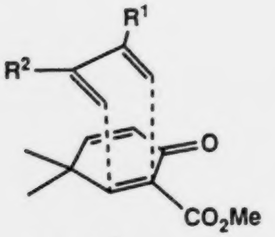

37

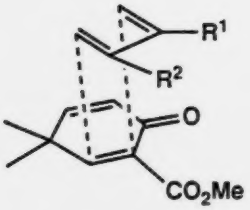


33 **34** **35**

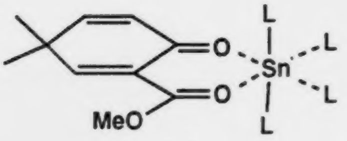
BF_3•OEt_2	30 : 70
$SnCl_4$	82 : 18



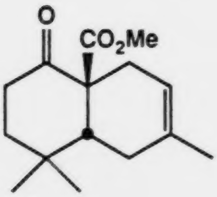
34A R^1=H, R^2=Me
35A R^1=Me, R^2=H



34B R^1=H, R^2=Me

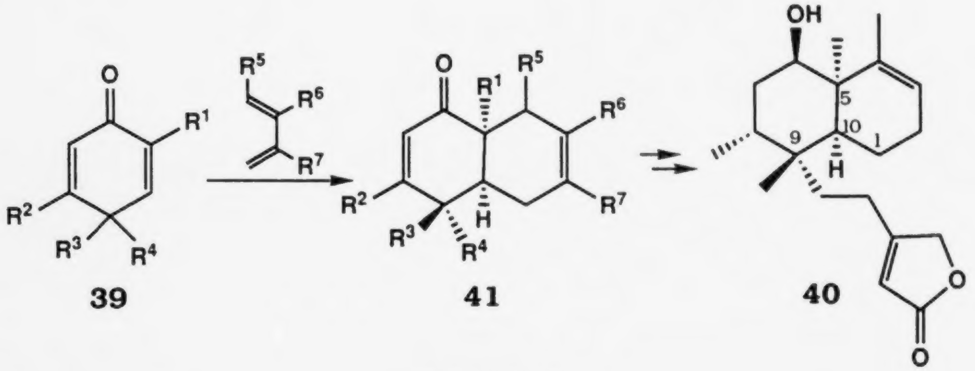


36



38

Whereas 2-cycloalkenones[128] activated with an additional electron-withdrawing group at the C_2 position (e.g, **33** and **37**) have been found to be good dienophiles, little is known about the facial selectivity of 4,4-disubstituted compounds possessing nonequivalent substituents such as in general structure **39**. In approaches to the total synthesis of diterpenoids of the *cis*-clerodane family, the Diels-Alder cycloaddition of dienophile **39** presents itself as an attractive route. Since in virtually all of the natural *cis*-clerodanes, the stereochemistry of the three contiguous chiral centers (C_5, C_9 and C_{10}) to be created by the Diels-Alder reaction is arranged in a special manner as shown in solidago lactone IV (**40**),[129] the facial selectivity is crucial to the success of the Diels-Alder approach. On the basis of steric grounds,[40] it is expected that the addition of a diene to **39** should be subjected to steric control, i. e., if R^4 is bulkier than R^3, the diene attack should occur preferentially from the sterically less hindered R^3 face, affording octalones of general structure **41**. If R^4 is a properly functionalized substituent, then the octalone intermediate **41** would possess the stereochemical requirements for the construction of *cis*-clerodane diterpenoids (Scheme 4).



Scheme 4

cis-Clerodanes are a novel class of diterpenes which have been found in nature in rapidly increasing numbers.[130,131] According to the stereochemistry of the A-B ring juncture, *cis*-clerodanes can be divided into two subgroups, namely, *cis*-normal-clerodane (5α,10α-*cis*-clerodane) and *cis*-ent-clerodane (5β,10β-*cis*-clerodane) as illustrated in Figures 4 and 5, respectively. In spite of the opposite stereochemistries at C_5, C_9 and C_{10}, they are usually diastereomeric rather than enantiomeric because both have α- C_8 methyl groups.

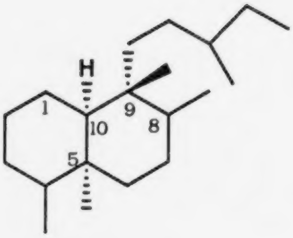


Figure 4

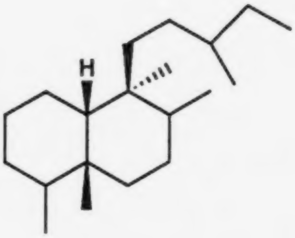
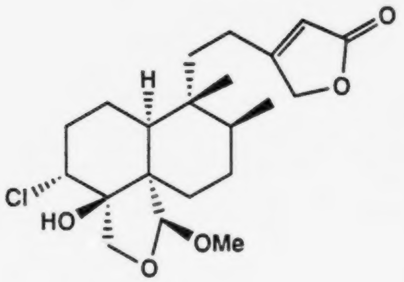


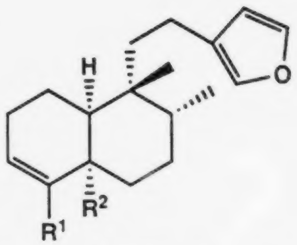
Figure 5

The structure of the first *cis*-clerodane from compositae, gutrierolide (**42**),[132] was determined by X-ray analysis. Perhaps prompted by this finding and the growing number of *cis*-clerodanes isolated from other plants, the absolute stereochemistries of the next reported pair of solidago clerodanes,[133] solidagoic acid A (**43**) and B (**44**), and a related series of neutral clerodanes[134] were studied exhaustively. Initially, an attempt was made to correlate **43** with hardwichiic acid (**45**),[135] a *trans*-clerodane with established stereochemistry. Comparison of **46** (derived from solidagoic acid A according to Scheme 5) with **47** (derived from **45**) revealed significant differences in the ^{1}H nmr chemical shifts, proving the nonequivalence of the two parent structures. Attempts were then made to correlate **43** with plathyterpenone (**48**)[133], a *cis*-clerodane of known absolute stereochemistry. Oxidation of **46** with Sarratt reagent gave enone **49**. Comparison of the CD (circular dichroism) results for **49** and **48** suggested a *cis*-A-B ring-fusion at C_5 and C_{10} identical to **48**. Therefore, **43** and **44** were assigned to have a $5\alpha,10\alpha$-*cis*-ring juncture indicating a normal labdane origin.

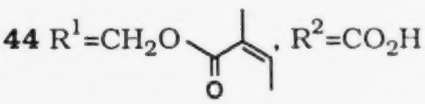


H
O
Cl
HO
OMe
O
O

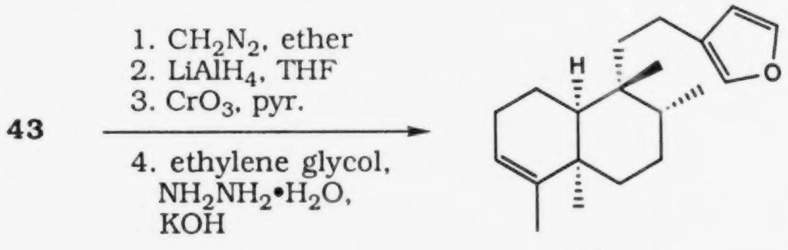
42



43 R^1=Me, R^2=CO_2H



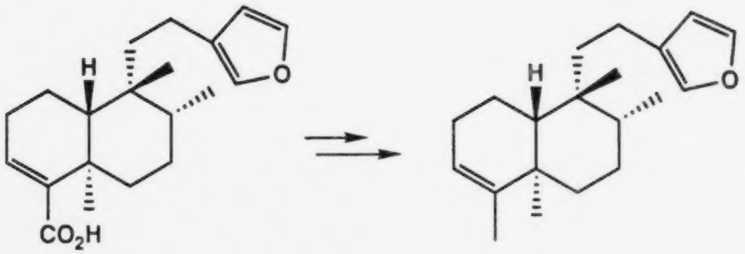
44 R^1=CH_2O , R^2=CO_2H



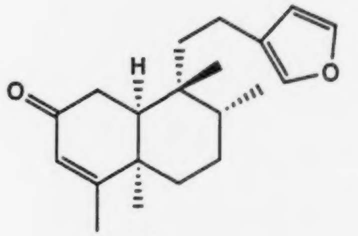
43
1. CH_2N_2, ether
2. $LiAlH_4$, THF
3. CrO_3, pyr.
4. ethylene glycol, $NH_2NH_2 \bullet H_2O$, KOH
H
O

46

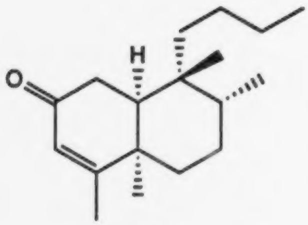
Scheme 5



45 **47**

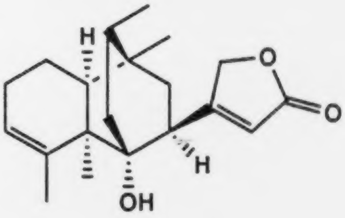


49
Negative Cotton
Effect (α -46)

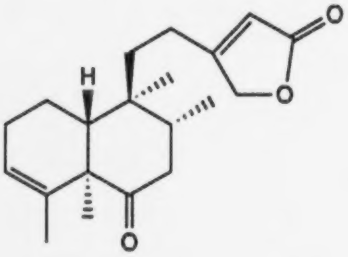


48
Negative Cotton
Effect (α -33)

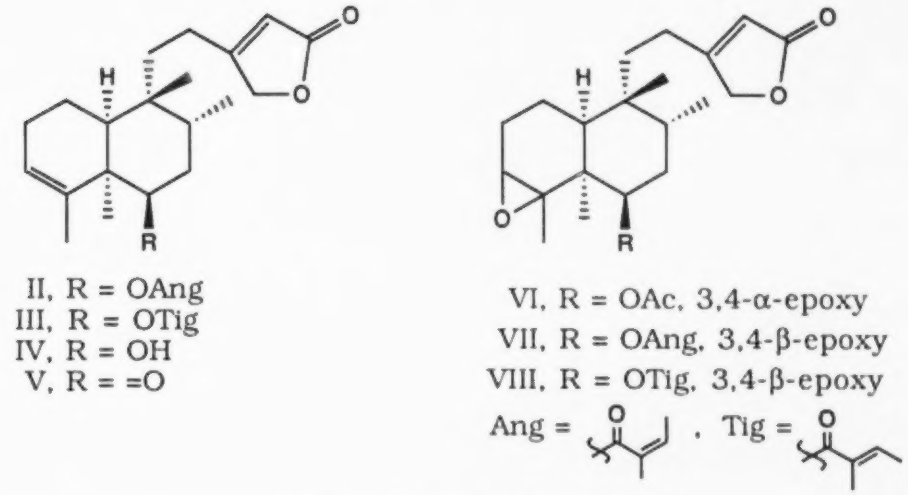
Prompted by the identification of tricyclosolidagolactone **50**, a *cis*-normal-clerodane from *S. altissima*,[136] Niwa and Yamamura reinvestigated the bitter principle of *S. altissima*. They proposed that the biogenesis of **50** involved a precursor that was constitutionally identical to the first proposed structure for solidagolactone V (**51**) but belonging to the *cis*-clerodane class. The reinvestigation consequently revised the structures of solidagolactones II-VIII (Figure 6) and the corresponding elongatolides (proposed by McCrindle and Okazaki as *trans*-ent-clerodanes[137,138]) to *cis*-normal-clerodanes.[129] The absolute stereochemistry of the solidagolactone series was confirmed by X-ray analysis of the C_6 bromobenzoate derivative of desacylsolidagolactone VIII.[139]



50



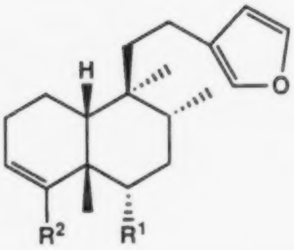
51


II, R = OAng
III, R = OTig
IV, R = OH
V, R = =O

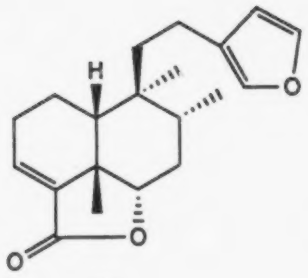
VI, R = OAc, 3,4-α-epoxy
VII, R = OAng, 3,4-β-epoxy
VIII, R = OTig, 3,4-β-epoxy
Ang = , Tig =

Figure 6. solidagolactones

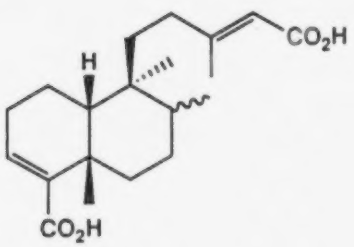
A group of *cis*-ent-clerodanes (**52**-**57**)[140] were isolated from *S. arguta*. The absolute stereochemistry of these compounds was confirmed by X-ray analysis[141] and chemical interconversions.[142] First, a nonheavy atom X-ray analysis of **57** established the relative stereochemistry. Then lactone **57** was transformed chemically into the co-occurring compounds **55** and **56**. Finally a study of the optical data for compound **52** confirmed the absolute stereochemistry of these structures and other compounds of similar structures such as haplopappic acid (**58**)[143], cistodioic acid (**59**) and related compounds. It was observed that the CD data for haplopappic acid, *S. arguta* clerodanes and the cistodioic acid related structure series had a common relative pattern which was largely opposite to those for solidagoic acid A and B. For example,



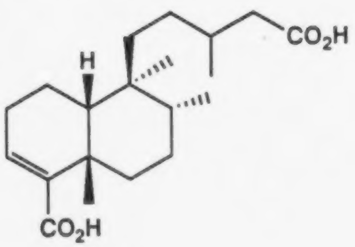
52 R^1 =H, R^2 = Me
53 R^1 = H, R^2 = CH_2OH
54 R^1 = H, R^2 = CH_2OAc
55 R^1 = OH, R^2 = CH_2OH
56 R^1 = OH, R^2 = CH_2OAc



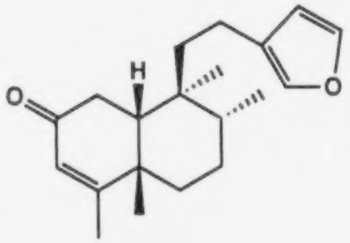
57



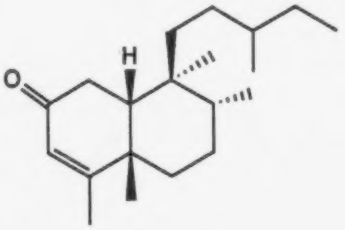
58



59



60
Positive Cotton
Effect (α +65)

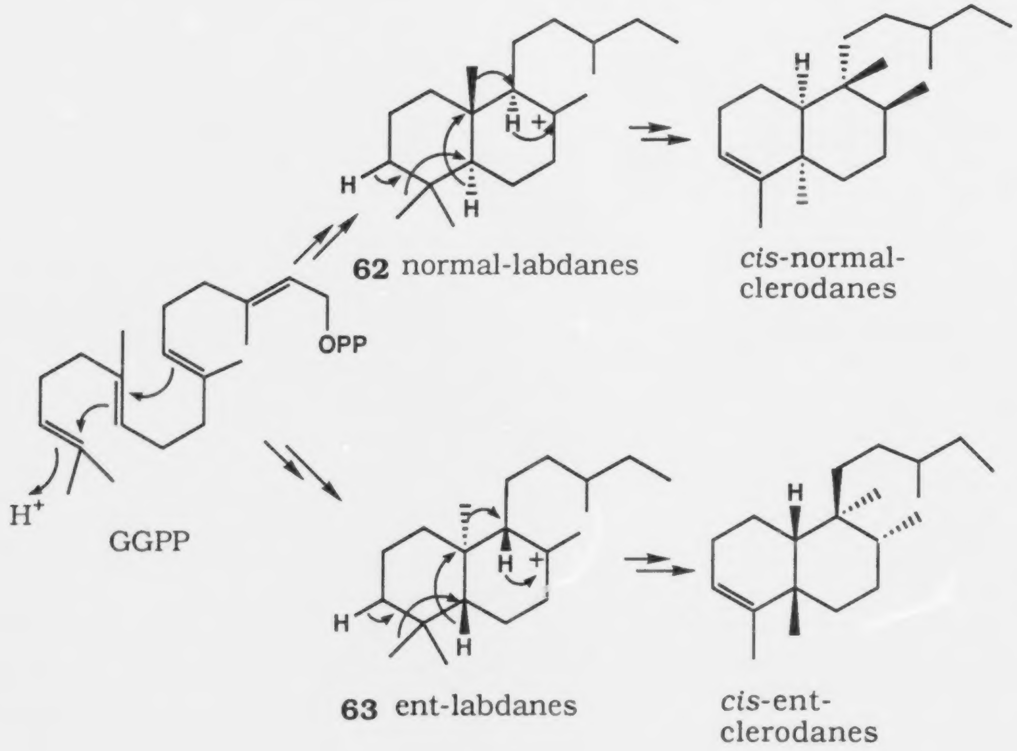


61
Positive Cotton
Effect (α +64)

the two enones, **60** and **61** derived from compound **52** and cistodioic acid (**59**), have positive Cotton effects for the n-π* transition of nearly equal amounts of amplitude (α +65 and α +64, respectively). On the other hand, plathyterpenone **48** and enone **49** derived from solidagoic acid A have an opposite and weaker Cotton effect (α -46 and α -33).[133]

Although there are no direct biosynthetic studies of *cis*-clerodanes, they must share the general biosynthetic pathway for diterpenes as illustrated in Scheme 6. Starting from geranyl geranyl pyrophosphate (GGPP), enzyme catalyzed cyclization results in normal-labdane and ent-labdane skeletons **62** and **63**. Subsequent rearrangements of **62** and **63** give normal- and ent-*cis*-clerodanes, respectively.

cis-Clerodanes often show interesting biological activities. Solidago clerodanes are usually described as the bitter principle of the root tissue and act as natural antifeedant. Solidagolactones have been reported to show potent piscicidal activities against killifish.[139] From the agricultural point of view, clerodanes (including *cis*-clerodanes) are potential pesticides with high efficacy and low toxicity. There have been considerable current interests in searching for natural pesticides like clerodanes and their analogues.[144]

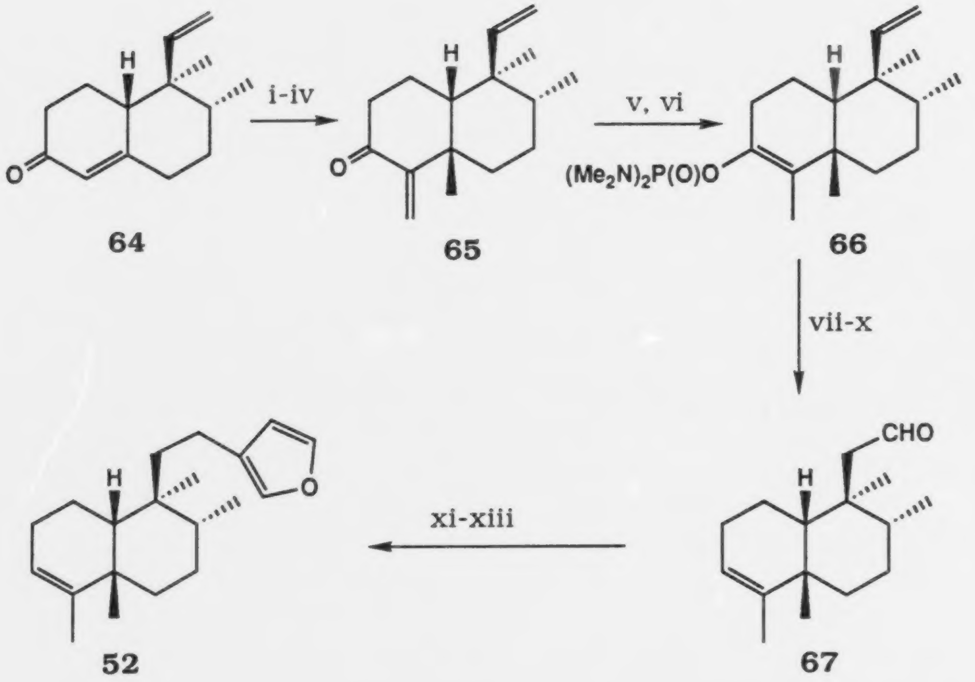

H
H +
H
H
62 normal-labdanes
cis-normal-clerodanes
OPP
H+
GGPP
H
H +
H
H
63 ent-labdanes
cis-ent-clerodanes

Scheme 6

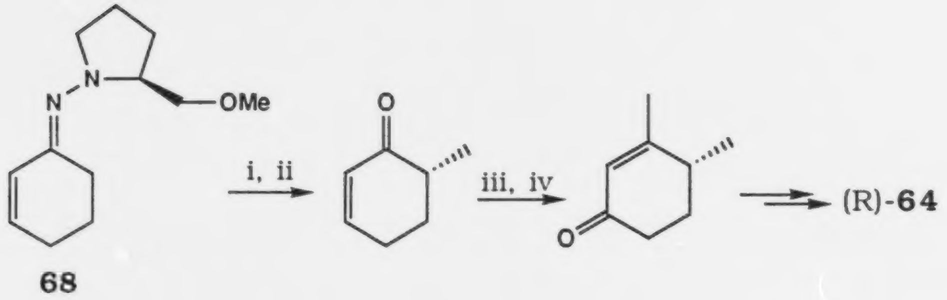
The large number of *cis*-clerodanes present in nature, the interesting biological activities and the challenging chemical structures have prompted three total syntheses, two formal total syntheses and a formal asymmetric synthesis of *cis*-clerodanes by a Japanese research group. In 1983, Tokoroyama and coworkers[145] reported the first total synthesis of a *cis*-clerodane, 15,16-epoxy-*cis*-cleroda-3,13(16),14-triene (**52**). The key intermediate in the synthesis was the octalone derivative **64** which was readily prepared from 3,4-dimethyl-2-cyclohexenone in an overall 60%

yield. The introduction of the C_5 angular methyl group was accomplished by 1,4-addition of methyllithium cuprate (Me_2CuLi). Trapping the enolate with formaldehyde followed by converting the resulting alcohol to mesylate and subsequent elimination using DBU gave intermediate **65**. 1,4-Reduction of **65** using lithium tri-sec-butylborohydride followed by trapping the enolate with $(Me_2N)_2POCl$ afforded intermediate **66**. Selective hydroboration followed by reduction of the phosphorodiamidate moiety and Swern oxidation gave aldehyde **67**. Addition of 3-furyllithium to the aldehyde followed by acetylation and reductive cleavage of the resulting acetate moiety using lithium in liquid ammonia gave the natural compound **52** in an overall yield of 3% from **64** (Scheme 7).

In 1987, Tokoroyama and coworkers[146] reported the preparation of the octalone intermediate **64** in an optically pure form. The key step involved the Ender's asymmetric alkylation of cyclohexenone (S)-amino-2-(methoxymethyl)-pyrrolidine (SAMP)-hydrozone **68** with methyl iodide, which gave 6-methyl-2-cyclohexenone (Scheme 8). Subsequent methyllithium addition to the ketone carbonyl followed by PCC oxidation gave (R)-3,4-dimethyl-2-cyclohexenone which was converted into intermediate **64**. Therefore, a formal asymmetric synthesis of compound **52** was achieved.

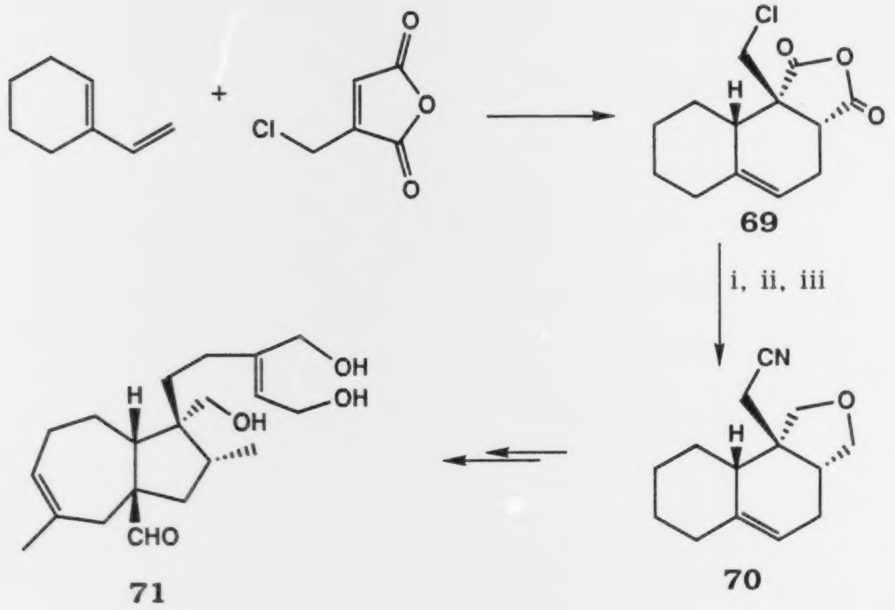

H
i-iv
O
64
H
O
65
v, vi
(Me2N)2P(O)O
H
66
vii-x
H
O
52
xi-xiii
CHO
H
67

Scheme 7. Reagents. i, Me_2CuLi; ii, HCHO; iii, $MeSO_2Cl$, Et_3N; iv, DBU; v, $LiB(CHMeEt)_3H$; vi, $(Me_2N)_2POCl$, Et_3N; vii, B_2H_6; viii, H_2O_2, NaOH; ix, Li, $EtNH_2$, *t*-BuOH; x, Me_2SO, $(COCl)_2$, then Et_3N; xi, 3-furyllithium; xii, Ac_2O, pyridine; xiii, Li, liq. NH_3.


N
N
OMe
68
i, ii
O
iii, iv
O
(R)-64

Scheme 8. Reagents. i, *i*-Pr_2Li, THF, then *p*-TsOMe; ii, MeI, then 2 M HCl, pentane; iii, MeLi, ether; iv, PCC, CH_2Cl_2.

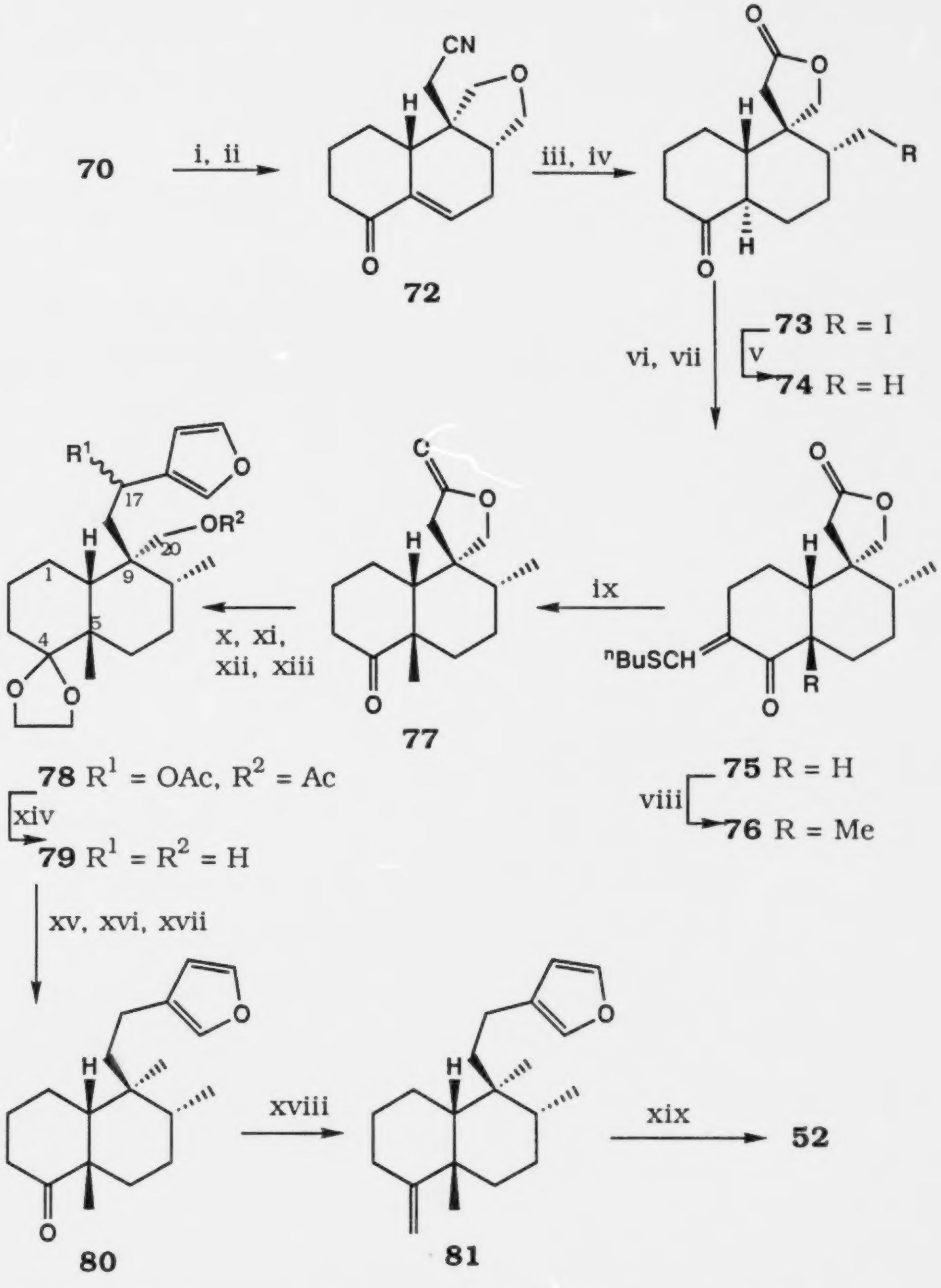
The most recent synthesis of compound **52** by Tokoroyama and coworkers[147] utilized a completely different scheme. The synthesis started from the Diels-Alder reaction of 1-vinylcyclohexene with (chloromethyl)maleic anhydride.[148] The resulting adduct **69** was converted to intermediate **70** which was previously used in the synthesis of portulal (**71**)[149] (Scheme 9), a diterpene with the *cis*-clerodane substitution pattern and a rearranged A-B ring system.



Scheme 9. Reagents. i, $LiAlH_4$; ii, TsCl, pyridine; iii, NaCN, NaI.

Starting from **70**, key synthetic operations towards **52** involved: (1) the introduction of the *cis* angular group at C_5, (2) construction of the side chain by appendage of a 3-furyl ring and deoxygenation at

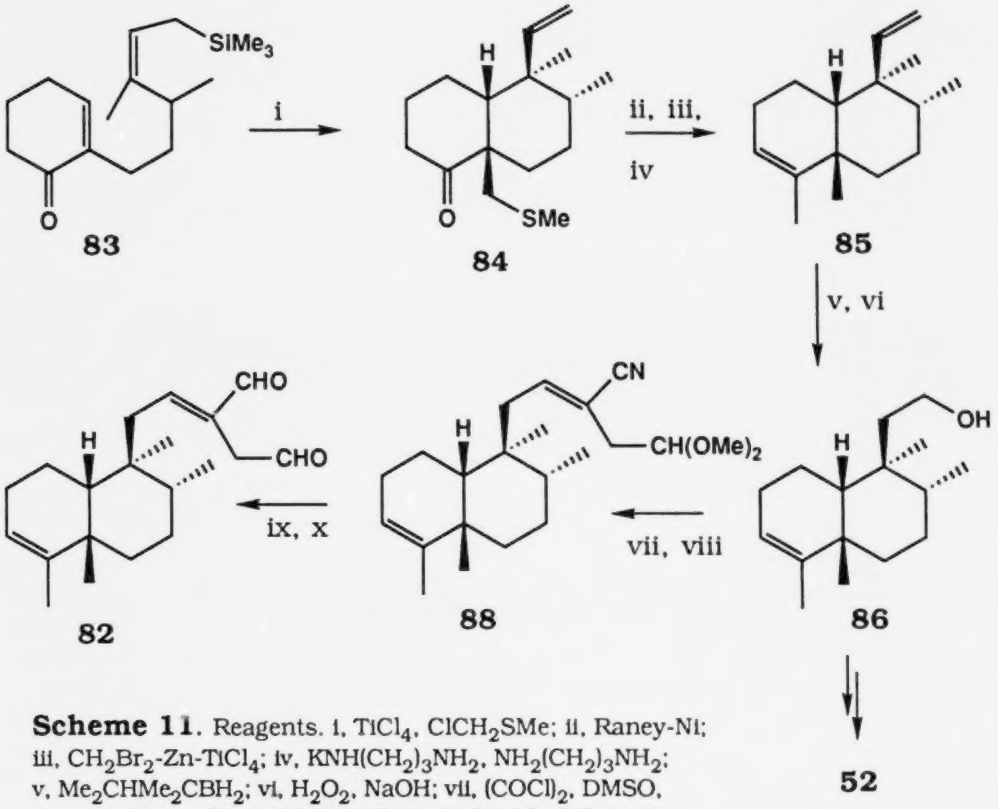
C_{17} and C_{20} to form methyl groups, and (3) elaboration of a vinyl methyl group in ring A from a C_4 carbonyl group. Allylic oxidation of **70** with selenium dioxide followed by MnO_2 oxidation of the resulting alcohol gave enone **72**. Catalytic hydrogenation followed by treatment of the resulting ketone with hydroiodic acid in acetic acid gave iodide **73** *via* regioselective cleavage of the tetrahydrofuran ring and concomitant hydrolysis of the cyano group. Reduction of the iodide with zinc in acetic acid gave the intermediate **74**. Initial attempts to introduce the angular methyl group by carbene addition to compound **74** were not successful. The problem was eventually solved by alkylating **75** using Ireland's procedure with methyl iodide and a large excess of potassium *t*-pentyloxide (25-30 eq !), furnishing the methylated compound **76** in 74% yield. Deprotection of **76** by alkaline hydrolysis afforded keto lactone **77**. The appendage of the side chain was accomplished by addition of 3-furyllithium to the acetal derived from lactone **77**, reduction of the resulting alcohol with sodium bis(2-methoxyethyl)aluminum hydride and subsequent acetylation, giving compound **78**. Reduction of **78** with lithium in liquid ammonia yielded **79**. Deoxygenation of the C_{20} carbon furnished ketone **80**. The last phase of the synthesis was the introduction of a vinyl methyl group in ring A from compound **80**. Difficulties were encountered in methylation with various organometallic reagents. However, the problem was circumvented by using Nozaki's reagent,


70
i, ii
72
iii, iv
73 R = I
v
74 R = H
vi, vii
75 R = H
viii
76 R = Me
ix
77
x, xi,
xii, xiii
78 R1 = OAc, R2 = Ac
xiv
79 R1 = R2 = H
xv, xvi, xvii
80
xviii
81
xix
52
CN
H
O
R
nBuSCH
OR2
17
20
1
9
4
5

Scheme 10. Reagents. i, SeO_2; ii, MnO_2; iii, H_2, Pd-C; iv, 57% HI-H_2O, P, AcOH; v, Zn, AcOH; vi, HCO_2Et, NaH; vii, *n*-BuSH, *p*-TsOH; viii, MeI, *t*-$C_5H_{11}OK$; ix, H_2O, KOH, $HOCH_2CH_2OH$; x, $HOCH_2CH_2OH$, *p*-TsOH; xi, 3-furyllithium; xii, $NaAl(OCH_2CH_2OMe)_2H_2$; xiii, Ac_2O, pyridine; xiv, Li, liq. NH_3; xv, CrO_3•2pyridine; xvi, NH_2NH_2•H_2O, KOH, $HOCH_2CH_2OH$; xvii, 1 M HCl; xviii, Zn-CH_2Br_2-$TiCl_4$; xix, $KNH(CH_2)_3NH_2$.

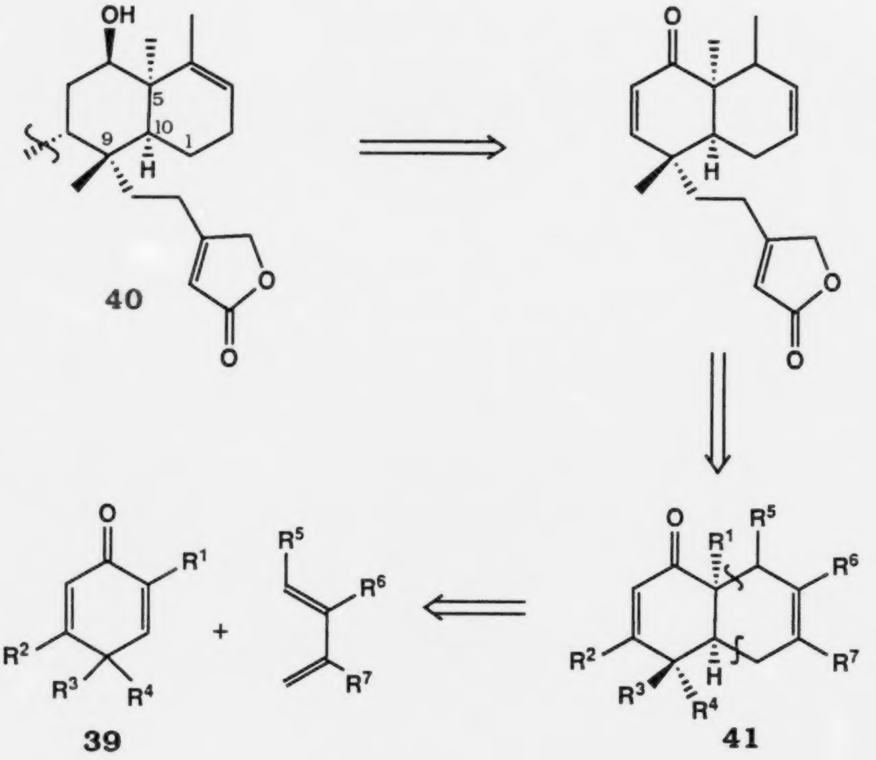
affording compound **81** which was isomerized to the natural product by Brown's procedure.

The total synthesis of another *cis*-clerodane, linaridial (**82**) was reported by the same research group in 1987.[150] The key operation of the synthesis differed from the other examples in that the *cis*-clerodane skeleton was constructed by means of stereocontrolled cyclization of diene **83** under $TiCl_4$ catalysis[151] followed by trapping of the metal enolate with a reactive electrophile, chloromethyl methyl sulfide, to give compound **84**. After reduction of the sulfide by Ra-Ni, the C_4 vinylic methyl was introduced in a similar fashion as the previous discussed synthesis, yielding compound **85**. Selective hydroboration of **85** afforded intermediate **86** which was used in this formal synthesis of natural product **52**. Starting from **86**, Swern oxidation followed by Horner-Smith condensation of the resulting aldehyde with **87** gave compound **88**. Subsequent reduction of the cyano group and hydrolysis of the acetal moiety afforded linaridial (**82**).



Scheme 11. Reagents. i, $TiCl_4$, $ClCH_2SMe$; ii, Raney-Ni; iii, CH_2Br_2-Zn-$TiCl_4$; iv, $KNH(CH_2)_3NH_2$, $NH_2(CH_2)_3NH_2$; v, $Me_2CHMe_2CBH_2$; vi, H_2O_2, NaOH; vii, $(COCl)_2$, DMSO, then Et_3N; viii, $(EtO)_2POCH(CN)CH_2CH(OMe)_2$ **87**) ,NaH; ix, DIBAL, Et_2AlCl; x, 1 M HCl.

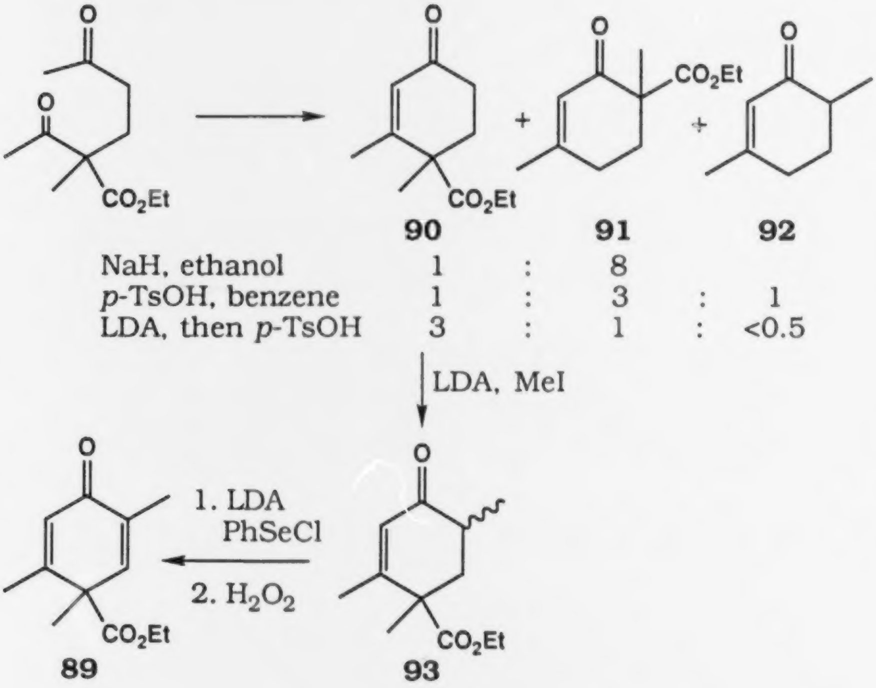
As outlined in the retrosynthetic analysis in Scheme 12, (using solidagolactone IV as an example), our approach to the *cis*-clerodane system differs primarily in the construction of the *cis*-bicyclic A-B ring system. Our primary strategy is to develop a general synthetic protocol which would permit the assembly of a variety of *cis*-clerodane diterpenes, especially the polyoxygenated ones, *via* a common intermediate **41**. Since in virtually all of the natural *cis*-clerodanes, the stereochemistry of the three contiguous chiral centers (C_5, C_9 and C_{10}) to be induced by the Diels-Alder cycloaddition is arranged in a special manner as shown in solidagolactone IV, the facial selectivity is crucial to the success of the Diels-Alder approach. As a result, we have carried out an extensive study on the facial selective Diels-Alder reactions of dienophiles of general structure **39**, and the application of these reactions towards the synthesis of natural clerodane diterpenes has also been carried out. The results will be discussed in the following section.


OH
5
10
9
1
H
O
40
O
H
O
O
O
R1
R2
R3
R4
39
+
R5
R6
R7
O
R1
R5
R6
R2
R7
R3
H
R4
41

Scheme 12

Results and Discussion

Dienone **89** was first briefly explored. It was prepared from the known enone ester **90**[152] according to Scheme 13. When the intramolecular aldol condensation was carried out by a modified literature procedure using sodium hydride in ethanol,[152] compounds **91** and **90** were obtained in a 8:1 ratio. When the condensation was performed under acidic conditions (*p*-TsOH in refluxing benzene with azeotropic removal of water), compounds **90**, **91** and **92** were obtained in a 1:3:1 ratio. If the aldol process was carried out using LDA as base followed by dehydration, the desired enone ester **90** was obtained as the major product. The spectral data of compound **92** were compared with an authentic sample obtained from decarbethoxylation of **91**. The structures of **91** and **90** were assigned based on their ^{1}H nmr spectra. For **91**, the vinylic proton appeared at δ 5.90 as a complex multiplet, while the vinylic proton of **90** was displayed as a quartet at δ 5.91 with a coupling constant of 1.5 Hz. The assignments were further confirmed by an NOE study on compound **90**. Irradiation of the C_4 methyl group at δ 1.45 resulted in a 6% enhancement for the vinylic methyl group, indicating a vicinal relationship of the two methyl groups. Alkylation of **90** with LDA and methyl iodide gave compound **93** as a mixture of two epimers as indicated by the ^{1}H nmr spectrum. Phenylselenenylation of **93** using LDA and phenylselenenyl chloride followed by oxidative elimination using hydrogen peroxide[153] gave dienone ester **89** which displayed carbonyl absorptions at 1733 and 1672 cm^{-1} in the ir spectrum. In the ^1H nmr spectrum, the two vinylic protons appeared at δ 6.56 (q, J = 1.5 Hz) and 6.20 (q, J = 1.5 Hz), respectively. The two vinylic methyl groups were found at δ 1.98 (d, J = 1.5 Hz) and 1.80 (d, J = 1.5 Hz). The C_4 methyl group appeared at δ 1.48 as a sharp singlet. The ethoxy group can be recognized by the signals at δ 4.15 (m, 2 H) and 1.22 (t, J = 7 Hz, 3 H) . The mass spectrum displayed a molecular ion peak at m/z 208.1103 corresponding to the formula $C_{12}H_{16}O_3$.

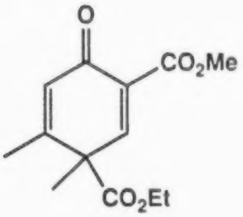


	90		91		92
NaH, ethanol	1	:	8		
p-TsOH, benzene	1	:	3	:	1
LDA, then *p*-TsOH	3	:	1	:	<0.5

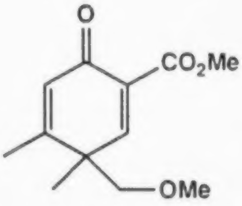
Scheme 13

When dienone ester **89** was treated with *trans*-piperylene using several Lewis acids ($SnCl_4$, $AlCl_3$, $FeCl_3$ and $ZnCl_2$) as catalysts, no reactions took place. In all instances, only the starting material was recovered. Obviously compound **89** was not sufficiently reactive as a dienophile.

Dienone ester **94** was envisaged to be a more suitable candidate as the replacement of the C_2 methyl in **89** by an electron-withdrawing group should enhance the dienophilicity of the C_2-C_3 double bond as predicted by the Alder's rule.[16,126] Unfortunately, attempted carbomethoxylation of compound **90** using dimethyl carbonate and sodium hydride resulted in extensive decomposition probably due to decarbethoxylation under the reaction conditions.

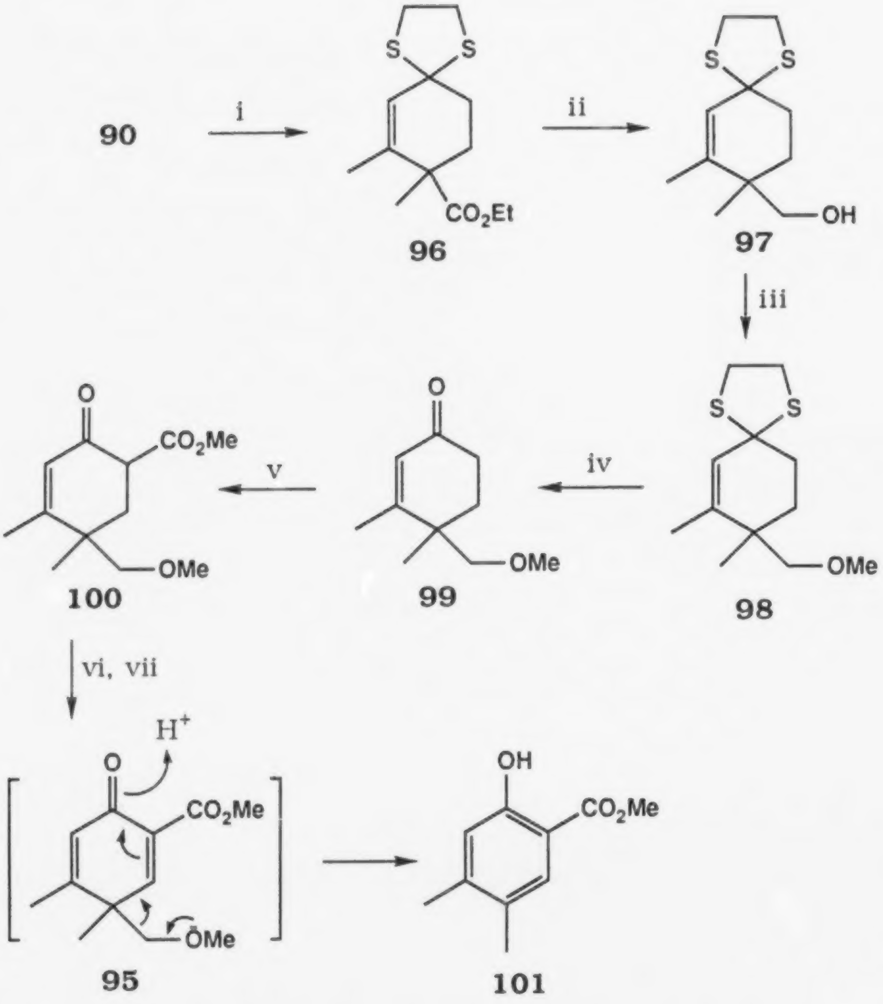


94



95

One possible solution to the problem would be to replace the carbethoxy group with methoxymethyl group as shown in structure **95**. Towards this end enone ester **90** was subjected to thioacetalization with 1,2-ethanedithiol and $BF_3 \bullet OEt_2$ to give thioacetal **96** in quantitative yield. Lithium aluminum hydride reduction of **96** gave alcohol **97** which was reacted with methyl iodide and sodium hydride, giving compound **98**.


90
i
96
ii
97
iii
98
iv
99
v
100
vi, vii
95
101
H⁺
CO2Et
OH
OMe
CO2Me
S
O

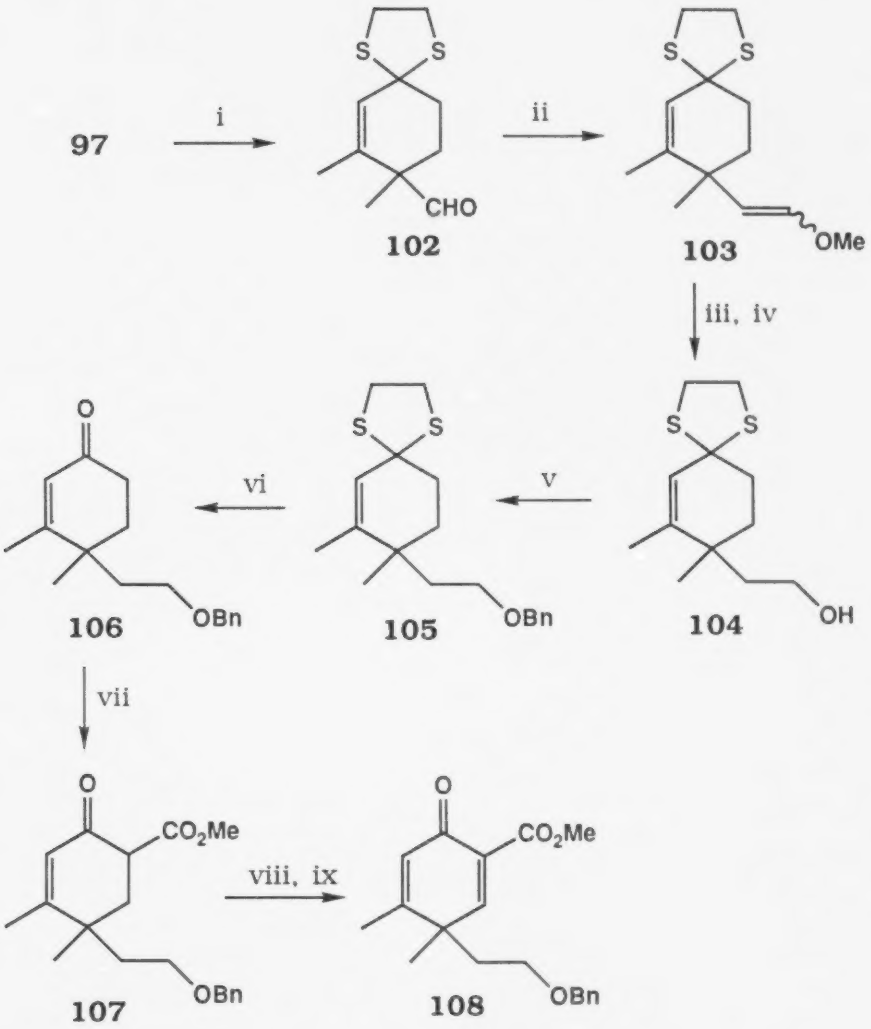
Scheme 14. i, $HSCH_2CH_2SH$, $BF_3{\bullet}OEt_2$; ii, $LiAlH_4$; iii, NaH, MeI; iv, Ag_2O, H_2O, MeOH; v, $(MeO)_2CO$, NaH; vi, PhSeCl, Pyridine; vii, H_2O_2.

Deprotection of the thioacetal group by silver oxide[154] afforded enone **99** whose ir spectrum showed a carbonyl absorption band at 1670 cm^{-1}. In the ^1H nmr spectrum, the vinylic proton appeared at δ 5.87 as a broad singlet. The methoxymethyl moiety could be easily recognized by the signals at δ 3.46 (d, *J* = 9 Hz), 3.16 (d, *J* =

9 Hz) and 3.34 (s, 3 H). The mass spectrum had a molecular ion peak at m/z 168.1149 in agreement with the formula $C_{10}H_{16}O_2$. Carbomethoxylation of **99** using dimethyl carbonate and sodium hydride afforded keto ester **100** as a mixture of three isomers (two epimers and the enol tautomer) since the ^1H nmr spectrum showed three vinylic proton signals at δ 5.92, 5.85 and 5.75. When the dehydrogenation of **100** was attempted *via* phenylselenenylation and oxidative elimination according to the method developed by Liotta *et al.*[155] the aromatization product **101** was formed presumably *via* the desired compound **95**. The results are outlined in Scheme 14.

At this point, we decided to extend the C_4 carbon chain since a two carbon unit like alkoxyethyl is required in the synthesis of *cis*-clerodanes. Starting from alcohol **97**, PCC oxidation of the primary alcohol gave aldehyde **102** in 83% yield. The aldehyde carbonyl absorption appeared at 1724 cm^{-1} in the ir spectrum. In the ^1H nmr spectrum, the singlet at δ 9.42 was attributed to the aldehydic proton. The vinylic proton was at δ 5.86 as a quartet (J = 1.5 Hz). The vinylic methyl appeared at δ 1.65 (d, J = 1.5 Hz) and the C_4 methyl was at δ 1.29 as a sharp singlet. The mass spectrum showed a molecular ion peak at m/z 228.0640 corresponding to the formula $C_{11}H_{16}OS_2$. Chain elongation was accomplished in a three step sequence according to Scheme 15. Wittig reaction of aldehyde **102** with methoxymethyltriphenylphosphonium chloride and *n*-

BuLi afforded enol ether **103** in 65% yield as a mixture of two isomers. Hydrolysis of **103** with concentrated hydrochloric acid followed by reduction of the resulting aldehyde with sodium borohydride gave alcohol **104** in 60% overall yield. The ir spectrum of compound **104** showed a hydroxy absorption at 3260-3415 cm^{-1}. In the ^1H nmr spectrum, the vinylic proton appeared at δ 5.59 as a broad singlet. The multiplets at δ 3.52-3.78 were attributed to the methylene protons of the hydroxyethyl group. The vinylic methyl was at δ 1.69 as a doublet (J = 1.5 Hz). In the mass spectrum, the molecular ion appeared at m/z 244.0959 indicating formula $C_{12}H_{20}OS_2$. Benzylation of alcohol **104** with benzyl bromide and sodium hydride gave compound **105** in 85% yield. Dethioacetalization was achieved using $HgCl_2$-$CaCO_3$ in aqueous acetonitrile,[156] furnishing enone **106** in 80% yield. The ir spectrum of **106** showed an enone carbonyl absorption band at 1665 cm^{-1}. In the ^1H nmr spectrum, the benzyl signals appeared at δ 7.31 (m, 5 H) and 4.48 (s, 2 H). The vinylic proton was at δ 5.30 as a quartet with a coupling constant of 1 Hz. The doublet at δ 1.80 (J = 1 Hz) was attributed to the vinylic methyl. The sharp singlet at δ 1.19 corresponded to the C_4 methyl. The molecular ion peak at m/z 258.1623 in the mass spectrum was in agreement with the molecular formula $C_{17}H_{22}O_2$. Carbomethoxylation of **106** with dimethyl carbonate and sodium hydride in refluxing DME afforded keto ester **107** in 85% yield.

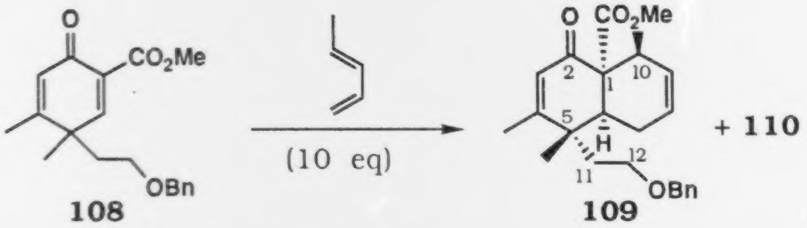

97
i
102
ii
103
iii, iv
104
v
105
vi
106
vii
107
viii, ix
108

Scheme 15. i, PCC on alumina; ii, $Ph_3P^+CH_2OMeCl^-$, *n*-BuLi; iii, conc. HCl; iv, $NaBH_4$; v, BnBr, NaH; vi, $HgCl_2$-$CaCO_3$, H_2O; vii, $(MeO)_2CO$, NaH; viii, PhSeCl, pyridine; ix, H_2O_2.

Dehydrogenation of **107** employing Liotta's procedure[155] gave dienone ester **108** in 75 % yield. The ir spectrum of **108** showed two carbonyl absorptions at 1741 (C=O, ester) and 1668 cm^{-1} (C=O, enone). In the ^1H nmr spectrum, the two vinylic protons appeared at δ 7.54 (s) and 6.21 (q, J = 1.5 Hz). The methoxy methyl was at δ 3.82 as a sharp singlet, and the other two methyl groups were at δ 2.00 (d, J = 1.5 Hz) and 1.34 (s). In the mass spectrum, the molecular ion was at m/z 314.1513, in agreement with the required formula $C_{19}H_{22}O_4$.

With dienone ester **108** in hand, we then went on to study its Diels-Alder reaction. *trans*-Piperylene was chosen as the diene as its reaction with **108** could give rise to adduct **109** which could serve as an intermediate for the synthesis of naturally occurring compounds of the *cis*-clerodane family. Aluminum chloride, ferric chloride and stannic chloride were selected as catalysts as it had been observed previously that these Lewis acids were suitable for related dienophiles. As shown by the results summarized in Table 2, these Lewis acids gave rather poor yields of the Diels-Alder adducts **109** and **110**. The reaction of enone ester **108** with *trans*-piperylene catalyzed by aluminum chloride gave a 45% yield of adducts, while the same reaction catalyzed by ferric chloride afforded products in 60% yield. When the reaction was catalyzed by stannic chloride, neither the Diels-Alder adducts nor the starting material was obtained. It therefore appeared that these Lewis acids could cause the decomposition of either the starting material or the products. Consequently, a weaker Lewis acid, zinc chloride, was explored. Although the reaction was slower, a much higher yield of the Diels-Alder adducts was obtained. Besides, no extensive decomposition of either the starting material or the products was observed. It was further noticed that when the amount of zinc chloride was increased, the rate of the reaction was enhanced accordingly.

Table 2. Diels-Alder reaction of **108** with *trans*-piperylene.



catalyst	solvent	temp (°C)	time (h)	yield (%)	ratio
$AlCl_3$ (1.0)	CH_2Cl_2	0	5	45	~5:1
$FeCl_3$ (1.2)	CH_2Cl_2	0	1	60	~5:1
$SnCl_4$ (1.3)	CH_2Cl_2	0	2	0	----
$ZnCl_2$ (1.2)	CH_2Cl_2	24	24	30[a]	~8:1
$ZnCl_2$ (2.0)	CH_2Cl_2	24	24	73[b]	~8:1
-------	Xylene	200	24	20[c]	~5:1

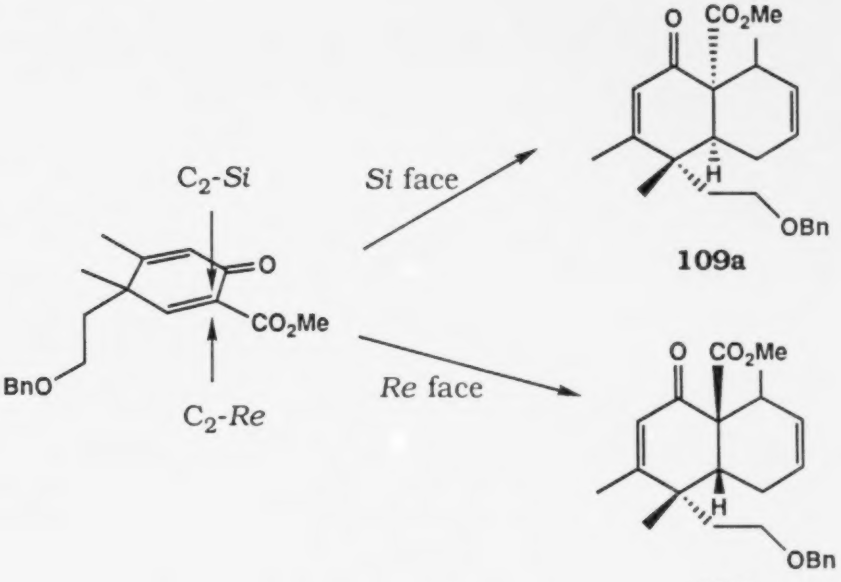
[a] Starting material was recovered in 57%.

[b] Starting material was recovered in 16%.

[c] Starting material was recovered in 60%

Although zinc chloride has been used as catalyst in Diels-Alder reactions,[157-164] its superiority in the present studies is noteworthy. There seems to be a trend that the yield of the Diels-Alder adducts **109** and **110** is inversely proportional to the order of the Lewis acidity: $AlX_3 > FeX_3 > SbX_5 > SnX_4 > ZnX_2$[165] with the exception of stannic chloride. In general, the stronger the Lewis acid used, the lower the yield. These results may be attributed to the instability of the highly functionalized dienophile **108** or its Diels-Alder adducts under strongly acidic conditions.

In all cases examined, the ratio (8:1-5:1) of the two adducts did not change significantly. In theory, the addition of *trans*-piperylene to dienone ester **108** could give rise to eight possible stereoisomers. However, on the basis of the *cis*-principle and the *ortho*-rule, the addition could lead to adduct **109a** or **111** depending upon whether the reaction occurs from the sterically less hindered *Si*-face or the sterically more hindered *Re*-face of the dienophile (Scheme 16). Prior to the present study no experimental evidence was available concerning the facial selectivity of this particular type of Diels-Alder reaction, although *a priori* it must resemble cases studied by Liotta, *et al.*[111] That is to say, the reaction course should be under the control of the steric factors and the favored adduct should be **109a**, resulting from the addition from the sterically less hindered *Si*-face.



Scheme 16

The structure of the major product was established to be **109** by spectroscopic methods. The mass spectrum showed a molecular ion at m/z 382.2147 corresponding to the formula $C_{24}H_{30}O_4$. In the ir spectrum, two carbonyl absorption bands were observed at 1726 (C=O, ester) and 1681 cm^{1} (C=O, enone). The ^{13}C nmr spectrum displayed two carbonyl signals at δ 195.592 and 174.590. The C_4 carbon appeared at δ 160.870 which was in-phase with the $CDCl_3$ signal. To determine the regiochemistry, extensive ^1H decoupling experiments were carried out and the ^1H nmr assignments are summarized in Table 3. From the coupling pattern of the H_6 (dd, J = 10, 7 Hz), it is clear that this compound is the *ortho*-adduct. In order to determine the stereochemistry, an NOE experiment was carried out. As shown in Figure 7, irradiation of the C_5 methyl resulted in a 3.12% enhancement for the C_{10} methyl group, indicating a *cis*-relationship for these methyl groups. The major adduct was therefore assigned to structure **109** on the basis of the expected *endo* addition of *trans*-piperylene to **108**. This assignment was further confirmed in a similar system as will be discussed later on. The structure of the minor adduct **110** could not be determined unambiguously since it could not be obtained in pure form, although it could be recognized as the Diels-Alder adduct from the ^1H nmr spectrum of the crude reaction mixture.

Table 3. ^1H nmr data for adduct **109**.

proton	δ (in ppm)	multiplicity (*J* in Hz)
C_6H_5-	7.35	m
$C_6H_5CH_2O$-	4.50, 4.55	2 d (14)
H_3	5.83	q (1.5)
H_6	2.74	dd (10, 7)
$H_{7\beta}$	1.97	dm (20)
$H_{7\alpha}$	2.19	dm (20)
H_8	5.49	ddd (10, 7, 3)
H_9	5.57	ddd (10, 4.5, 2)
H_{10}	2.74	m (7, 7, 4)
H_{11a}	1.85	m
H_{11b}	1.69	ddd (14, 9, 6)
H_{12}	3.58-3.74	m

C_4 methyl	1.84	d (1.5)
C_5 methyl	1.12	s
C_{10} methyl	1.25	d (7)
methoxy	3.69	s

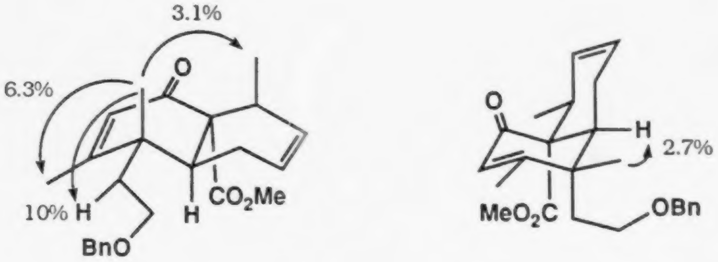
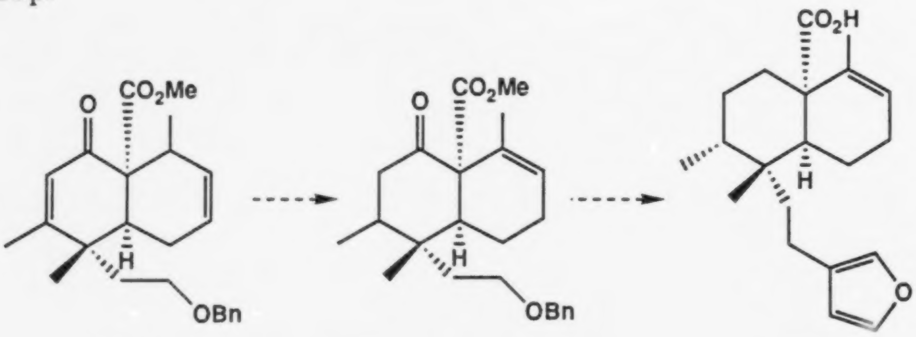


Figure 7

The above result was the first example concerning the facial selectivity of conformationally mobile 4,4-dialkylsubstituted 1,5-cyclohexadienone in the Diels-Alder reaction. It demonstrated that an excellent chemical yield (90% based on consumed dienophile using $ZnCl_2$ as catalyst), good *endo/exo* selectivity and good π-facial selectivity (≥5-8:1) could be obtained from this type of system.

The effective application of this approach to the synthesis of *cis*-clerodane diterpenes such as solidagoic acid (**43**) requires the selective reduction of the C_3-C_4 double bond as illustrated in Scheme 17. This reduction process could be problematic due to the following reactions. The most popular method, catalytic hydrogenation,[166] is not suitable here as the C_8-C_9 double bond would be reduced indiscriminately. Hydrosilylation using

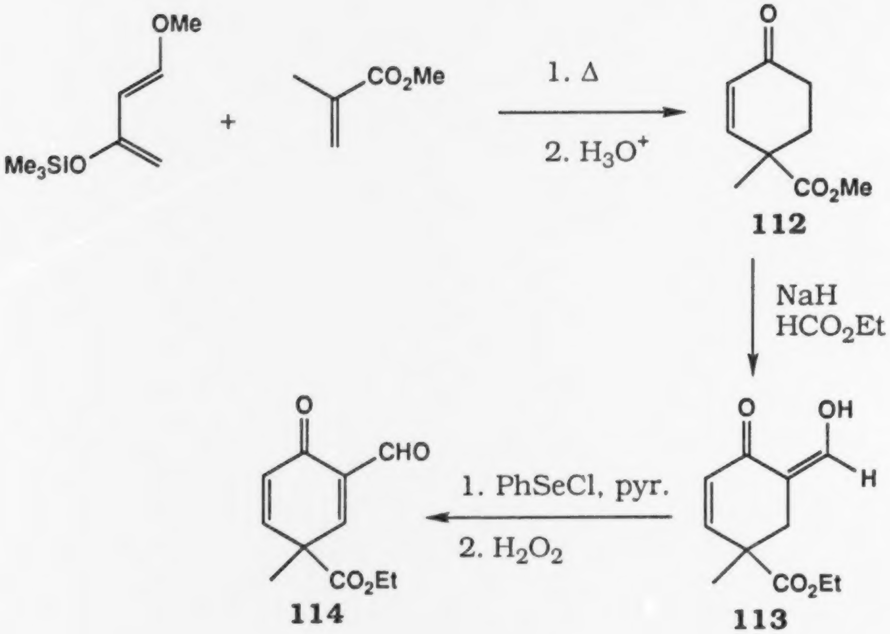
Wilkinson's catalyst[166] is the method of choice in selective reduction of α,β-unsaturated carbonyl compounds in the presence of non-conjugated double bonds. However, β-disubstituted α,β-unsaturated carbonyl compounds are inert to the reaction conditions. The dissolving metal reduction was then considered.[167] It is possible to selectively reduce the conjugated double bond using this method. Complications could arise from other functional groups such as the ester group and the benzyl group.



109 **43**

Scheme 17

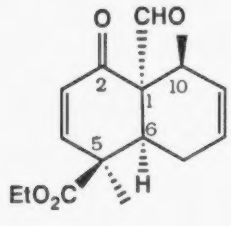
Enone ester **112** was then chosen as it could avoid the potential problems encountered for **89**. Compound **112** was prepared by Danishefsky *et al* [168] from Danishefsky's diene and methyl methacrylate in 70% overall yield according to Scheme 18. When we carried out the reaction in a sealed tube at 90°C using a four-fold excess of methyl methacylate (in the literature a four-fold excess of diene was used), enone ester **112** was obtained in quantitative yield after acid treatment of the adduct. Since the carbomethoxylation of enone ester **90** using sodium hydride and dimethylcarbonate resulted in extensive decomposition, we could foresee the same problem for enone ester **112**. Therefore, we turned our attention to the much milder formylation process.[169] When **112** was reacted with a large excess of ethyl formate and 2 equivalents of sodium hydride, compound **113** was formed quantitatively. Apparently a transesterification process had also taken place. Compound **113** existed completely in the enol form as indicated by the ^{1}H nmr spectrum. Dehydrogenation of **113** according to the procedure by Liotta *et al* afforded the highly functionalized dienophile **114** in 85% yield (Scheme 18). The ir spectrum for **114** showed carbonyl absorptions at 1736 (C=O, ester), 1709 (C=O, aldehyde) and 1669 cm^{-1} (C=O, enone). In the ^{1}H nmr spectrum, the sharp singlet at δ 10.25 was attributed to the formyl proton. The three vinylic protons appeared at δ 7.80 (d, J = 3 Hz), 7.25 (dd, J = 10, 3 Hz) and 6.35 (d, J = 10 Hz). Obviously there is a W-coupling between the H_3 proton and the H_5 proton. The singlet at δ 1.65 was attributed to the C_4 methyl group. The mass spectrum did not show the molecular ion. However, the base peak at m/z 135.0448 corresponded to $[M-CO_2Et]^+$. The chemical ionization mass spectrum showed a $[M+NH_4]^+$ peak at m/z 226.


OMe
Me3SIO
+
CO2Me
1. Δ
2. H3O+
O
CO2Me
112
NaH
HCO2Et
O
CHO
CO2Et
114
1. PhSeCl, pyr.
2. H2O2
O
OH
H
CO2Et
113

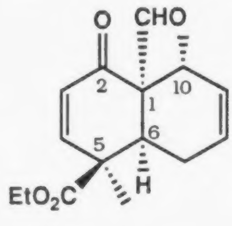
Scheme 18

Dienone ester **114** reacted slowly with *trans*-piperylene at room temperature (4 days). It reacted much faster in refluxing benzene (24 hours), affording a single spot on TLC. The ^1H nmr spectrum of the product obtained in 95% yield however revealed that two compounds in a ratio of 4.5:1 were formed as indicated by the signals at δ 9.66 and 9.85. Besides, a very small signal (< 2% according to the integration) at δ 9.45 was also observed. The ir spectrum of the mixture showed carbonyl absorption bands at 1727 cm^{-1} and 1690 cm^{-1}. The mass spectrum displayed a molecular ion at m/z 276.2364 indicating the formula $C_{16}H_{20}O_4$. Besides, the base peak appeared at m/z 247.1332 ($C_{15}H_{19}O_3$) due to the loss of the formyl group from the molecular ion.

To facilitate the assignment of the ^1H nmr spectrum and to determine the regio- and stereochemistry, the following experiments were carried out. First, extensive ^1H decoupling experiments were performed. The results are summarized in Table 4. It was very clear that the reaction between dienone ester **114** and *trans*-piperylene followed the normal "*ortho*" rule as the the regiochemistries for both the major compound **115** and the minor compound **116** could be easily determined by the H_6 coupling patterns. For the major compound, a W-coupling between the H_6 proton and the H_4 vinylic proton was observed. Therefore, the ddd coupling pattern suggested the presence of two adjacent protons for H_6. For the minor compound, the H_6 proton appeared as a doublet of doublets with two equal coupling constants of 6 Hz each again indicating that two protons were adjacent. To determine the stereochemistry, NOE experiments were carried out. Irradiation of the C_5 methyl at δ 1.45 and 1.46 for both compounds resulted in enhancement for both signals at δ 9.85 and 9.66 (Figures 8 and 9), indicating that the C_5 methyl and the formyl group in each compound must be on the same face. Further irradiation of the H_6 protons at δ 3.00 and 2.97 resulted in enhancement for both formyl protons (Figures 8 and 9). Therefore, the ring juncture of each compound must be *cis* as expected on the basis of the *cis*-principle. Furthermore, the same irradiation resulted in a 4% enhancement of the H_{10} proton for the major adduct and a 2.7% enhancement of the C_{10} methyl for the minor adduct (Figures 8 and 9). From these results, the orientation of the C_{10} methyls for both compounds could therefore be determined.


O
CHO
2
10
1
6
5
EtO$_2$C
H

115


O
CHO
2
10
1
6
5
EtO$_2$C
H

116

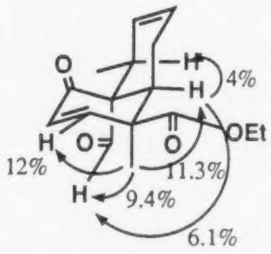

O
H
4%
H
H
O
O
OEt
12%
11.3%
H
9.4%
6.1%

Figure 8

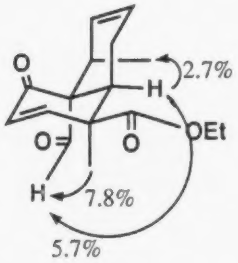

O
2.7%
H
O
O
OEt
H
7.8%
5.7%

Figure 9

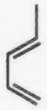
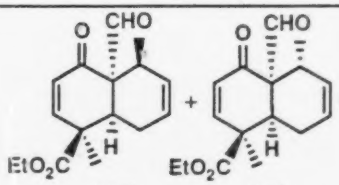
Table 4. ^{1}H nmr data for adducts **115** and **116**.

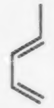
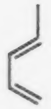
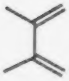
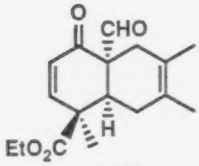
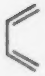
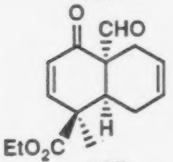
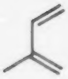
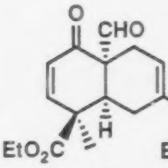
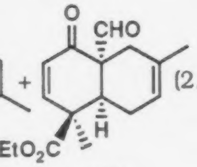
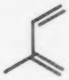
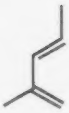
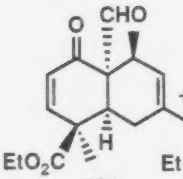
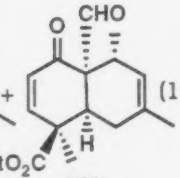
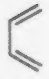
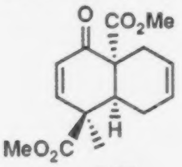
115			**116**	
δ (in ppm)	multiplicity (*J* in Hz)	proton	δ (in ppm)	multiplicity (*J* in Hz)
5.98	d (10)	H_3	6.02	d (10)
6.86	dd (10, 2)	H_4	6.84	d (10)
3.00	ddd (10, 6, 2)	H_6	2.97	dd (6, 6)
2.05	ddddd(18,10, 3, 2, 2)	$H_{7\beta}$		

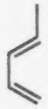
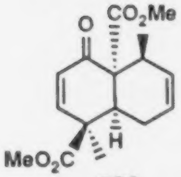
2.20	ddddd (18, 6, 2, 2, 2)	$H_{7\alpha}$		
5.50	ddd (10, 6, 3)	H_8		
5.59	ddd (10, 4, 2)	H_9		
2.71	m (6, 3, 7, 2)	H_{10}	3.15	m
9.66	s	formyl-H	9.85	s
1.46	s	C_5-Me	1.45	s
1.28	d (7)	C_{10}-Me	1.17	d (7)

The π-facial selectivity observed for the reaction between dienone ester **114** and *trans*-piperylene was intriguing and unexpected. The exclusive addition of diene to the ester face of **114** could hardly be explained by steric interactions of the geminal substituents with the approaching diene experienced in the transition state. To further study the facial diastereoselectivity of **114**, its reaction with a number of dienes under a variety of conditions were explored. The results are summarized in Table 5.

Table 5. Diels-Alder reactions of **114** and **123** with dienes.

entry	dieno-phile	diene	catalyst (eq)^a	temp (°C)	time (h)	yield (%)^b	product (ratio)
1	**114**		------	78	24	95	 (4.5:1) **115** **116**

2	**114**		$ZnCl_2$ (3)	0	5	95	**115** + **116** (19:1)
3	**114**		$FeCl_3$ (2)	-78	2	60	**115**
4	**114**		------	78	45	60^c	 **117**
5	**114**		$ZnCl_2$ (3)	23	16	90	 **118**
6	**114**		------	78	42	30^d	 +  (2.2:1) **119** **120**
7	**114**		$ZnCl_2$ (3)	-20	24	90	**119** + **120** (4.7:1)
8	**114**		------	78	8	95	 +  (1:3) **121** **122** + two isomers (1:1, 5%)
9	**123**		$ZnCl_2$ (2)	23	16	95	 **125**

10	**123**		$ZnCl_2$ (2)	0	4.5	~100	 **126**

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[a] All Lewis acid catalysed reactions were carried out in dichloromethane. Benzene was used as the solvent for thermal reactions.

[b] Yields are based on the amount of starting material applied.

[c] The starting material was recovered in 30%.

[d] The starting material was recovered in 65%.

A. Addition to *trans*-piperylene

When a solution of dienone ester **114** was reacted with 10 equivalents of *trans*-piperylene using zinc chloride (3 eq) as catalyst at 0°C for 5 h (Table 5, entry 2), adducts **115** and **116** were formed smoothly in a ratio of 19:1 in 95% yield. Other isomers were formed in less than 2% as indicated by the ^{1}H nmr spectrum. In the ^{13}C APT spectrum, a total of 16 lines were observed for the major product. Six were in-phase and the rest were anti-phase with respect to the $CDCl_3$ signal. The formyl carbonyl was at δ 201.35. The enone and ester carbonyls were at δ 196.28 and 173.27, respectively. Four signals appeared at δ 147.23, 129.60, 123.71 and 123.07 indicating the presence of two double bonds.

It was speculated that increasing the amount of zinc chloride used in the reaction might enhance the complexation between zinc chloride and the ester carbonyl group, resulting in the increasing bulkiness of the ester group and consequently a reversal of the facial selectivity. However, when the amount of $ZnCl_2$ used was increased from 1.2 to 3 equivalents, the same results were obtained. Obviously the amount of Lewis acid used did not change the course of the reaction nor the facial selectivity. Other Lewis acids were also studied. The use of stannic chloride as catalyst resulted in extensive decomposition of the material even at -78°C. So did the use of ferric chloride at 0°C. However, when the reaction was carried out at -78°C, compounds **115** and **116** were obtained in 60% yield in a ratio better than 20:1 (Table 5, entry 3). Other isomers were not detected by the ^1H nmr spectrum.

B. Addition to 2,3-dimethyl-1,3-butadiene

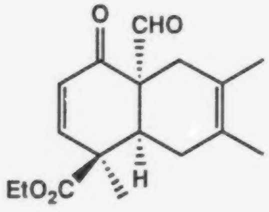
A solution of dienone ester **114** and excess diene in benzene was heated to reflux for 45 h. Flash chromatography gave adduct **117** in 60% yield along with the recovered starting material (30%). The ir spectrum of compound **117** showed two carbonyl absorption bands at 1730 and 1685 cm^{-1}. In the ^1H nmr spectrum, about 2% of another compound was present as indicated by the signal at δ 9.41. The ^1H nmr signals for adduct **117** are listed in Table 6. The ^{13}C APT spectrum displayed a total of 17 lines. The formyl carbonyl carbon was at δ 200.68 and was *anti*-phase with the $CDCl_3$ signal. The enone and ester carbonyl carbons were at δ 197.09 and

172.84, respectively . Four signals at δ 150.79, 126.54, 124.53 and 122.06 indicated the presence of two double bonds. The mass spectrum displayed a molecular ion at m/z 290.2521 corresponding to the formula $C_{17}H_{22}O_4$.

Table 6. ^{1}H nmr data for adduct **117**.

proton	δ (in ppm)	multiplicity (*J* = Hz)
formyl-H	9.60	s
H_3	6.02	d (10)
H_4	6.83	d (10)
H_6	2.85	dd (6, 5)
$H_{7\alpha}$	2.16	dm (18)
$H_{7\beta}$	2.01	dm (18)
$H_{10\alpha}$	2.28	br d (17)
$H_{10\beta}$	2.55	br d (17)
C_5-Me	1.47	s
C_8 ,C_9-Me	1.53, 1.63	m, m
EtO-	4.09	q (7)
	1.27	t (7)

The stereochemistry of **117** was determined by NOE experiments. Irradiation of C_5 methyl resulted in a 4% enhancement of the formyl proton. This indicated that the C_5 methyl and the formyl group were on the same face (Figure 10). Irradiation of the formyl proton at δ 9.60 resulted in a 6.1% enhancement of the H_6 angular proton. Therefore, the ring juncture must be *cis*.



117

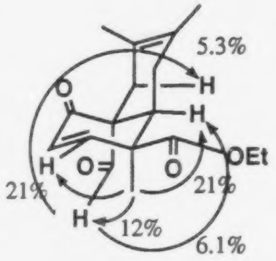
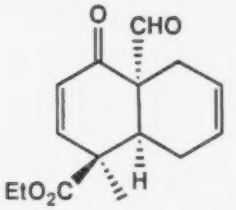


Figure 10

C. Addition to 1,3-butadiene

Dienone ester **114** did not undergo reaction with 1,3-butadiene at room temperature without Lewis acid catalysis. However, when zinc chloride was used as a catalyst, the reaction proceeded smoothly to give adduct **118** in 85% yield along with a 10% recovery of the starting material. The ir spectrum of **118** showed carbonyl absorptions at 1728 and 1687 cm^{-1}. The ^1H nmr spectrum resembled closely that of compound **117**. The formyl proton appeared at δ 9.62 as a sharp singlet. Four vinylic protons appeared at δ 6.84 (d, J = 10 Hz), 6.04 (d, J = 10 Hz), 5.66 (m) and 5.56 (m). The mass spectrum displayed a molecular ion peak at m/z 262.1200, in agreement with the formula $C_{15}H_{18}O_4$. The elemental analysis also supported the molecular composition. In the ^{13}C APT spectrum, a total of 15 lines were observed. The signal at δ 200.33 which was anti-phase to the $CDCl_3$ signal was attributed to the formyl carbonyl carbon. The enone and ester carbonyl carbons were observed at δ 196.88 and 172.77, respectively. Four signals at δ 150.79, 126.46, 125.71 and 122.60 indicated the presence of two double bonds. The stereochemistry of adduct **118** was determined again by NOE experiments. Irradiation of the C_5 methyl resulted in a 3.4% enhancement of the formyl proton (Figure 11). Irradiation of the H_6 proton resulted in a 9.6% enhancement of the formyl proton. Likewise, irradiation of the formyl proton caused a 7.9% enhancement of the H_6 proton. Therefore, the C_5 methyl, the formyl group and the H_6 proton must be *cis* to each other.



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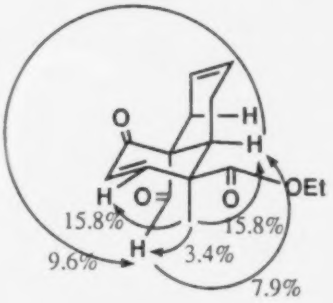


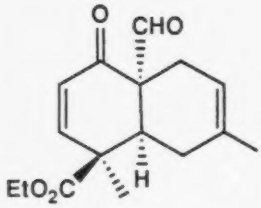
Figure 11

D. Addition to isoprene

The reaction between dienone ester **114** and isoprene in refluxing benzene was very sluggish. After 42 h of reaction time with a large excess (30 eq) of isoprene, only 30% of the Diels-Alder adducts were obtained along with recovered starting material. The ^1H nmr spectrum indicated that four compounds were formed in a ratio of 18:8:1:1. Structures **119** and **120** were assigned to the two major adducts after extensive ^{1}H decoupling studies and NOE experiments. The ^{1}H nmr data for **119** and **120** are summarized in Table 7. In the NOE experiment (Figure 12), irradiation of the C_5 methyls for both compounds at δ 1.49 and 1.48 resulted in a 9% enhancement for each of the formyl protons, indicating a *cis* relationship between the C_5 methyl and the formyl group in each compound.

Table 7. ^{1}H nmr data for **119** and **120**.

119			**120**	
δ (in ppm)	multiplicity (*J* in Hz)	proton	δ (in ppm)	multiplicity (*J* = in Hz)
6.02	d (10)	H_3	6.05	d (10)
6.80	d (10)	H_4	6.83	d (10)
2.88	dd (6.5, 5)	H_6	2.81	dd(6.5, 5.5)
2.18	dm (18)	$H_{7\alpha}$	2.26	dm (18)
2.02	dm (18)	$H_{7\beta}$	2.09	dm (18)
		H_8	5.24	m
5.35	m	H_9		
2.40	dm (18)	$H_{10\alpha}$	2.54	dm (18)
2.61	dm (18)	$H_{10\beta}$	2.61	dm (18)
9.60	s	formyl-H	9.59	s
1.49	s	C_5-Me	1.48	s
1.57	br s	C_8-Me		
		C_9-Me	1.67	br s



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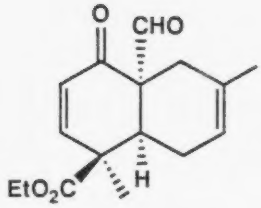


120

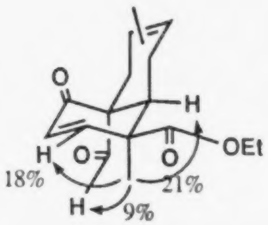


Figure 12

When zinc chloride was used as a catalyst, the reaction proceeded smoothly to give a 95% yield of adducts **119** and **120** in a ratio of ca. 5:1. Other isomers were absent as shown by the ^1H nmr spectrum. This observed enhancement of the regioselectivity was in accordance with the experimental results obtained by Liu and Browne on 4,4-dimethyl-1,5-cyclohexadienone systems.[125]

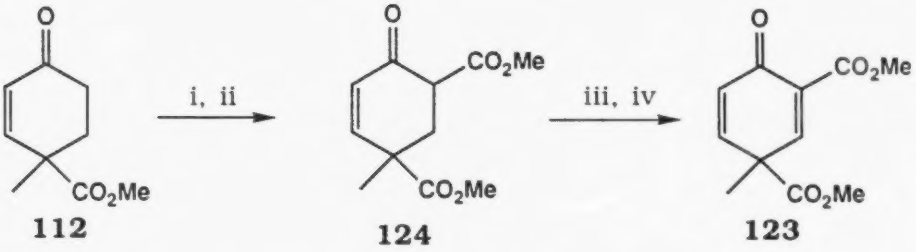
E. Addition to (*E*)-2-methyl-1,3-pentadiene

The reaction of dienone ester **114** and (*E*)-2-methyl-1,3-pentadiene in refluxing benzene was finished in 8 h, giving two major adducts **121** and **122** in a ratio of 1:3 in 95% yield. From the ^1H nmr spectrum, two minor isomers (1:1, 5%) were also formed. The mass spectrum of the mixture showed a molecular ion peak at m/z 294.1463 corresponding to the formula $C_{16}H_{22}O_5$. The ir spectrum had two carbonyl absorption bands at 1727 (C=O, ester and aldehyde) and 1687 cm^{-1} (C=O, enone). The ^1H nmr spectral data of **121** and **122** (Table 8) resembled those of compound **115** and **116**, respectively.

Table 8. ^{1}H nmr data for adducts **121** and **122**.

121			**122**	
δ (in ppm)	multiplicity (J in Hz)	proton	δ (in ppm)	multiplicity (J in Hz)
5.95	d (10)	H_3	6.00	d (10)
6.86	dd(10, 2)	H_4	6.80	d (10)
3.09	ddd(9, 7, 2)	H_6	2.94	dd (6, 4.5)
5.26	m	H_9	5.26	m
		$H_{10\alpha}$	2.66	m
3.02	m	$H_{10\beta}$		
9.65	s	formyl-H	9.85	s
1.45	s	C_5-Me	1.44	s
1.61	m	C_8-Me	1.57	br s
1.23	d (7)	C_{10}-Me	1.15	d (7)

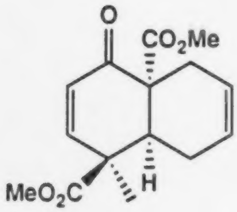
The overwhelming *syn* preference to the ester face observed for dienone ester **114** is unprecedented. It is also of interest to know the facial selection of dienone diester **123** in Diels-Alder reactions, although *a priori* it must be similar to that observed for compound **114**. The preparation of **123** is shown in Scheme 19. The difficulties of carbomethoxylation encountered for enone ester **90** was overcome by using Mander's reagent, methyl cyanoformate, a highly reactive acylating agent which has been used to selectively acylate highly functionalized carbonyl compounds.[170] When the acylation process was carried out using Mander's original procedure,[171] only a 40% of the keto ester **124** was obtained along with recovered starting material. However, when the process was carried out using the modified procedure by Zieglar *et al.*[172] compound **124** was obtained in 92% yield. The ^1H nmr spectrum indicated that three isomers (two epimers and an enol tautomer) were formed. The mass spectrum showed a molecular ion peak at m/z 226.0843, in agreement with the formula $C_{11}H_{14}O_5$.



Scheme 19. i, *i*-Pr_2NLi, then HMPA and $NCCO_2Me$; ii, NH_4Cl; iii, PhSeCl, pyridine; iv, H_2O_2.

Dehydrogenation using the standard procedure afforded 82% dienone diester **123** along with 14% recovered starting material **124**. The ir spectrum of compound **123** showed carbonyl absorptions at 1736 and 1670 cm^{-1}. In the ^1H nmr spectrum, a doublet at δ 7.71 (J = 3 Hz) was attributed to H_3. Two other vinylic protons were at δ 7.04 (dd, J = 10, 3 Hz) and 6.35 (d, J = 10 Hz). The two methoxy groups appeared at δ 3.88 and 3.78, and the C_4 methyl was at δ 1.61. The mass spectrum showed a molecular ion peak at m/z 224.0686 corresponding to the formula $C_{11}H_{12}O_5$.

The Diels-Alder cycloaddition of **123** with 1,3-butadiene using zinc chloride as catalyst proceeded smoothly to afford a quantitative yield of adduct **125**. Other compounds were formed in less than 2% as indicated by the ^{1}H nmr spectrum. The ir spectrum of compound **125** showed carbonyl absorptions at 1735 (C=O, esters) and 1688 cm^{-1} (C=O, enone). The mass spectrum had a molecular ion peak at m/z 278.1153 corresponding to the formula $C_{15}H_{18}O_5$. The ^{1}H nmr spectrum of **125** was very similar to that of compound **118**. The data are summarized in Table 9. In the ^{13}C APT nmr spectrum, a total of 15 signals were observed. Seven signals were in-phase and eight were anti-phase with respect to the $CDCl_3$ signal. Three carbonyl signals appeared at δ 195.50, 173.62 and 173.13. Signals at δ 149.38, 126.11, 124.16 and 124.02 indicated the presence of two double bonds.



125

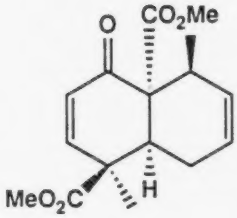
Table 9. ^1H nmr data for adduct **125**

proton	δ (in ppm)	multiplicity (*J* in Hz)
H_3	6.00	d (10)
H_4	6.73	dd (10, 0.5)
H_6	2.97	t (6)
$H_{7\alpha}$	2.17	dm (18)
$H_{7\beta}$	2.00	dm (18)
H_8	5.43	m
H_9	5.59	m
$H_{10\alpha}$	2.42	dm (17.5)
$H_{10\beta}$	2.63	dm (17.5)
OMe1	3.68	s
OMe2	3.60	s
C_5-Me	1.38	s

The reaction of **123** with *trans*-piperylene using zinc chloride as a catalyst gave adduct **126** in quantitative yield. The ir spectrum showed two carbonyl absorption bands at 1732 (C=O, esters) and 1693 cm^{-1} (C=O, enone). The mass spectrum exhibited a molecular ion peak at m/z 292.1307 corresponding to the formula $C_{16}H_{20}O_5$. The ^1H nmr spectrum of adduct **126** resembled closely that of compound **115**. Therefore, it was assigned as the *endo*-to-enone adduct resulting from addition of diene to the C_4 ester face. Less than 2% of other isomers were formed as indicated by the ^1H nmr spectrum. The assignments of the the ^1H nmr data were made by comparing with those of compound **115** and are summarized in Table 10. In the ^{13}C APT nmr spectrum, a total of 16 signals were observed. Six of them were in-phase and the rest were anti-phase with the $CDCl_3$ signal. Three carbonyl carbons appeared at δ 195.06, 174.15 and 173.94. Signals at δ 145.32, 130.66, 128.07 and 122.95 indicating the presence of two double bonds. The methoxy methyl carbons appeared at δ 52.50 and 52.31.

Table 10. ^1H nmr data for adduct **126**.

proton	δ (in ppm)	multiplicity (*J* in Hz)
H_3	5.95	d (10)
H_4	6.77	dd (10, 2)
H_6	3.06	ddd (9, 7, 2)
$H_{7\alpha}$	2.12	m
$H_{7\beta}$	1.85	m
H_8	5.39	ddd (10, 7, 3)
H_9	5.54	ddd (10, 4, 2)
H_{10}	2.72	m
C_5-Me	1.36	s
C_{10}-Me	1.25	d (7)
OMe1	3.73	s
OMe2	3.74	s



126

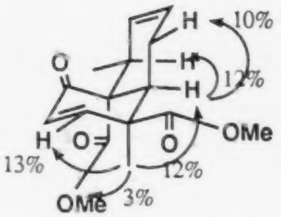


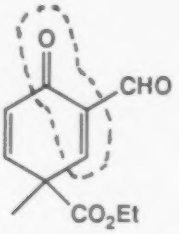
Figure 13

The stereochemistry of adduct **126** was further supported by NOE experiments. Irradiation of the C_5 methyl group resulted in a 3% enhancement for each of the methoxy groups, 12% enhancement for the H_6 proton and 13% enhancement for the H_4 vinylic proton. Irradiation of the H_6 proton resulted in 12% enhancement for the $H_{10\alpha}$ proton at δ 2.72 and 10% enhancement for the $H_{7\alpha}$ proton at δ 2.12 (Figure 13). The results obtained from addition of **123** with 1,3-butadiene and *trans*-piperylene are also compiled in Table 5.

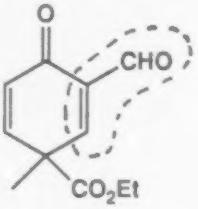
From the above discussion, it can be concluded that the change of a formyl group at the C_2 position of dienophile **114** into an ester group does not affect the the rate of the cycloaddition, the *endo*/*exo* selectivity or the facial selectivity of the addition.

An examination of the results in Table 5 reveals that the reaction of the dienone ester **114** with *trans*-piperylene and (*E*)-2-methyl-1,3-pentadiene occurred with different *endo*/*exo* stereoselectivities. As illustrated by structures **114a** and **114b**, there are in fact two dienophilic components in dienone ester **114**. These are the α,β-

unsaturated ketone (**114a**) and the α,β-unsaturated aldehyde (**114b**) moieties. Normally, it would be unnecessary to distinguish between these two moieties, except in cases where the *endo*-rule is in effect.

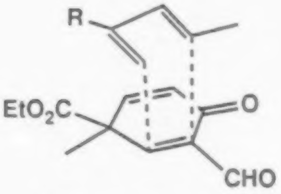


114a

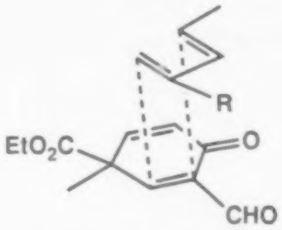


114b

Endo addition to the enone or to the α,β-unsaturated aldehyde moiety of **114** would give rise to stereochemically distinguishable products. The factor or factors determining which dienophilic moiety would dominate the reaction pathway is expected to be a function of the most effective secondary orbital overlap with the diene. It was observed that addition of *trans*-piperylene to dienone ester **114** occurred predominantly by secondary orbital overlap with the enone carbonyl (transition state **115a**, R = H). This is surprising because the *endo*-to-enone transition state **115a** is more hindered than the one *endo*-to-aldehyde **116a**. However, the apparent anomaly is understood when one examines the LUMO coefficients of the hypothetical formyl dienone (Figure 14).[111] It is clear that transition state **115a** incorporates larger stabilizing secondary orbital interactions than transition state **116a**. Lewis acids like zinc chloride and ferric chloride can further enhance this interaction, and consequently higher selectivity was observed (Table 4, entries 2, 3).



115a, R = H
121a, R = Me



116a, R = H
122a, R = Me

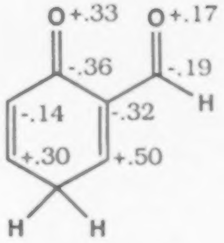
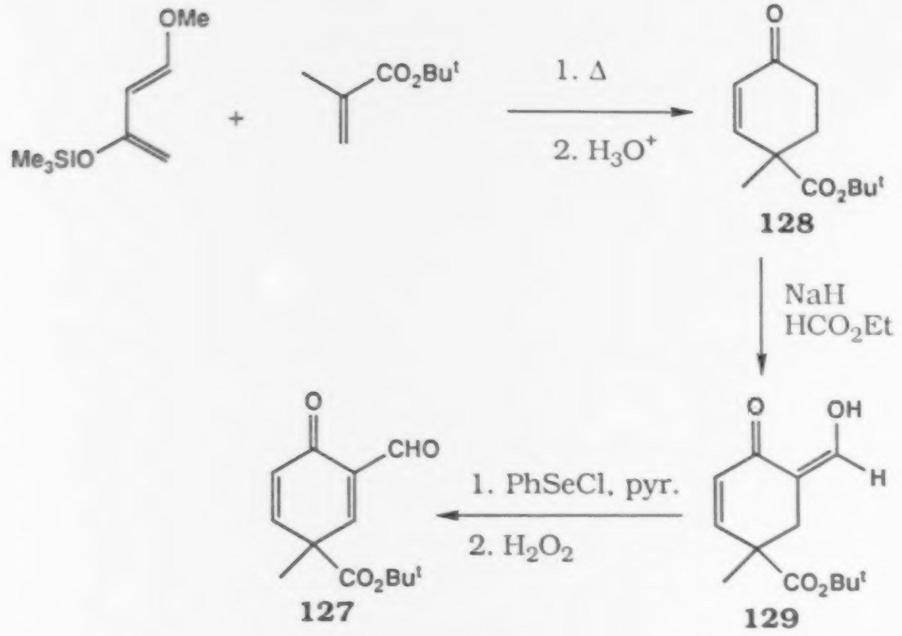


Figure 14

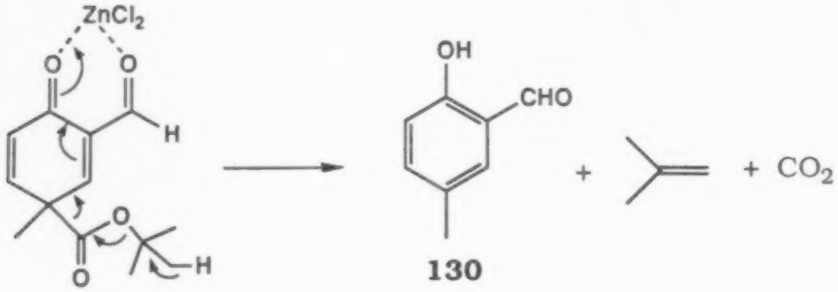
In the case of (*E*)-2-methyl-1,3-pentadiene, the favorable secondary orbital interactions of diene with the enone moiety in transition state **121a** (R = Me) can not compensate for the destabilization caused by the steric interaction between the C_2 methyl of the diene and the C_4 ester group of dienophile **114**. As a result, transition state **122a** is favored and compound **122** was obtained as the major product.

A further examination of the results summarized in Table 5 reveals a strong preference for addition from the ester side in all the cases, resulting in virtually exclusive formation of the corresponding adduct. This selectivity was totally unexpected in light of the relative van der Waals sizes estimated for carbomethoxy group (n = 12.1) methyl group (n = 8.5).[173] It therefore appeared that the observed π-facial selectivity was dominated by electronic factors. To prove or disprove that the steric interactions with the geminal substituents were the controlling factor in the course of the addition, dienone ester **127** was prepared and its reactions with 1,3-butadiene and *trans*-piperylene were studied. It was assumed that if the facial selectivity was controlled by steric factors, then a bulkier ester group such as a *t*-butyl ester would change the reaction course, giving rise to a totally different products distribution. Dienone ester **127** was prepared in a similar fashion as compound **114** (Scheme 20). Diels-Alder reaction of Danishefsky's diene and *t*-butyl methacrylate followed by acid hydrolysis gave enone ester **128**. The ir spectrum of **128** showed carbonyl absorptions at 1726 and 1688 cm^{-1}. The ^1H nmr spectrum was similar to that of enone ester **112** except for the *t*-butyl group which appeared as an intense singlet at δ 1.49. The mass spectrum showed a molecular ion at m/z 210.1245 corresponding to the formula $C_{12}H_{18}O_3$. The same procedure was used to introduce the formyl group which afforded compound **129**. Subsequent dehydrogenation gave dienone ester **127**. The ir spectrum of **127** showed carbonyl absorptions at 1716 (C=O, ester), 1704 (C=O, aldehyde) and 1674 cm^{-1} (C=O, enone). The ^1H nmr spectrum resembled closely that of dienone ester **124** except for the *t*-butyl group which appeared at δ 1.49 as a singlet. The mass spectrum did not give the molecular ion peak. However, a strong peak was displayed at m/z 135.0448 corresponding to the formula $C_8H_7O_2$ due to the loss of the *t*-butoxycarbonyl moiety from the molecular ion.


OMe
Me3SiO
+
CO2Bu^t
1. Δ
2. H3O+
O
CO2Bu^t
128
NaH
HCO2Et
O
OH
H
CO2Bu^t
129
1. PhSeCl, pyr.
2. H2O2
O
CHO
CO2Bu^t
127

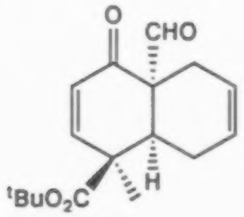
Scheme 20

Dienone ester **127** did not react with 1,3-butadiene in refluxing benzene. When the reaction was carried out at 0°C using zinc chloride as a catalyst, two compounds were formed in a ratio of 3:1. The major compound was identified as the aromatization product **130** by comparing its ^{1}H nmr spectral data with the literature value.[174] This is not surprising since Lewis acid such as zinc chloride can certainly facilitate the aromatization process as illustrated in Scheme 21.



130

Scheme 21



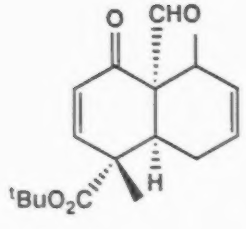
131

The minor compound was assigned to structure **131** since its ir, ^{1}H nmr and ^{13}C spectra closely resembled those of compound **118**. In the ir spectrum, carbonyl absorptions were observed at 1728 (C=O, ester and aldehyde) and 1681 cm^{-1} (C=O, enone). The ^{1}H nmr spectrum assignments are summarized in Table 11. In ^{13}C APT nmr spectrum, a total of 15 signals were observed. The aldehyde carbonyl carbon appeared at δ 200.38. Two other carbonyl carbons were at δ 196.53 and 171.99, respectively. The four signals at δ 151.14, 126.24, 126.13 and 122.83 indicated the presence of two double bonds. The *t*-butyl group was indicated by the signals at δ 82.46 and 27.92. The mass spectrum did not give the molecular ion peak. However, the peak at m/z 160.0878 corresponded to the formula $C_{11}H_{12}O$, which was due to the loss of the formyl and the *t*-butoxycarbonyl groups from the molecular ion. The foregoing experiment clearly suggested that the introduction of a bulkier ester group into the C_4 position of dienone ester **114** did not alter the π-facial selectivity significantly.

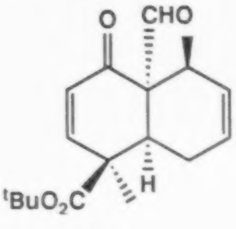
Table 11. ^1H nmr data for adduct **131**.

proton	δ (in ppm)	multiplicity (*J* in Hz)
Formyl-H	9.62	s
H_3	6.02	d (10)
H_4	6.86	dd (10, 0.5)
H_6	2.88	t (6)
H_7	2.22	m (2 H)
H_8	5.59	m
H_9	5.68	m
$H_{10\alpha}$	2.32	dm (18)
$H_{10\beta}$	2.69	dm (18)
C_5-Me	1.44	s
t-Butyl	1.47	s

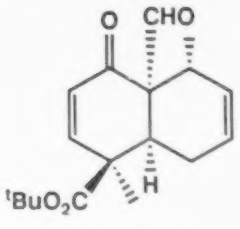
The above result was further substantiated by the thermal reaction of **127** with *trans*-piperylene. When the reaction was performed in refluxing benzene for 36 h using 10 equivalents of *trans*-piperylene, three compounds in a ratio of 9:2.6:1 were obtained in a combined yield of 95%. The ir spectrum of the mixture showed carbonyl absorptions at 1722 and 1689 cm^{-1}. The mass spectrum had a weak molecular ion peak at m/z 304.1692 indicating formula $C_{18}H_{24}O_4$. Besides, the peak at m/z 275.1649 corresponded to the formula $C_{17}H_{23}O_3$ as a result of cleavage of the formyl group from the molecular ion. Separation by chromatography gave first a fraction (8%) whose ^1H nmr spectrum differed significantly from those for adducts **115** and **116**. The formyl proton (δ 9.50) and the H_3-H_4 vinylic protons (δ 5.95, J = 10 Hz and δ 6.45, J = 10, 2 Hz) were upfield shifted substantially than those of adduct **115** and **116**. The most significant difference was the C_5 methyl group. For the present compound, the methyl was found at δ 1.33. Therefore, the compound was assigned to structure **132**. The observed chemical shift differences for the methyl groups could be rationalized as follows. For adducts **115** and **116**, the C_5 methyl is in the deshielding zone of the formyl carbonyl, resulting in downfield shift. The stereochemistry of **132** at C_{10} remains to be determined. Further elution gave the two major compounds as a mixture in 3.4:1 ratio. The ^1H nmr spectral data (Table 12) of the major and the minor components resembled closely those for adducts **115** and **116**, respectively. Therefore, they were assigned to structures **133** and **134**, respectively. The mixture turned into a sticky solid (m.p. 68-76°C) which gave satisfactory elemental analysis. Attempted recrystalization was not successful.



132



133

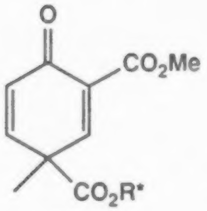


134

Table 12. ^{1}H nmr data for adducts **133** and **134**.

133			**134**	
δ (in ppm)	multiplicity (*J* in Hz)	proton	δ (in ppm)	multiplicity (*J* in Hz)
9.67	s	Formyl-H	9.84	s
5.95	d (10)	H_3	5.98	d (10)
6.82	dd (10, 2)	H_4	6.86	dd (10, 1)
2.96	ddd (9.5, 7, 2)	H_6	2.99	t (6)
2.69	m	H_{7a}	2.69	m
2.06	m	H_{7b}	2.06	m
5.51	ddd (10, 7, 3)	H_8	5.56	m
5.59	ddd (10, 4, 2)	H_9	5.63	m
2.69	m	H_{10}	3.10	m
1.49	s	*t*-Butyl	1.48	s
1.42	s	C_5 Me	1.41	s
1.28	d (7)	C_{10} Me	1.17	d (7)

Two conclusions can be drawn from the above experiment. First, The introduction of a bulkier ester group slowed down the reaction rate considerably (from 24 h for **114** to 36 h for **127**). This is readily understood in terms of steric interactions since *t*-butyl ester is certainly substantially bulkier than the corresponding ethyl ester. Second, the ratio of the product distribution was not significantly affected by the replacement of the C_4 ethyl ester in **114** by the *t*-butyl ester group. It was further observed in this laboratory that the reaction of dienone ester **135** with 1,3-butadiene using $ZnCl_2$ as a catalyst furnished two diastereomers **136** and **137** in a ratio of 1:1 in 94% yield.[175] Again, the addition of diene occurred exclusively from the C_4 ester face of dienone ester **135**. It was concluded from the aforementioned discussion that steric interactions did not play a major role in the Diels-Alder cycloaddition of dienone esters **114**, **123** and **127**.



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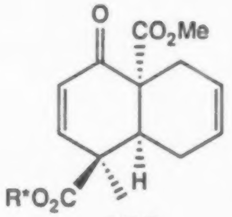
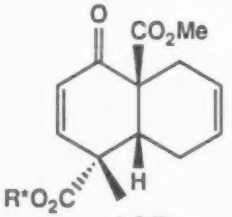
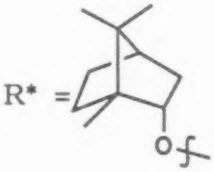


136



137



Among many other factors that could affect the facial selectivity, three factors seem to contribute to the unusually high selectivity. These are enone conformer population of **114**, electrostatic interactions of **114** and diene, and secondary orbital interactions of **114** and diene.

Dienone ester **114** probably exists in a shallow boat conformation with the ester group in a quasi-equatorial position due to two reasons (Figure 15). (a) In sacrificing the conjugation, the shallow boat conformation can avoid excessive ring strain experienced in a completely planar form. (b) The proposed conformation can avoid unfavorable electronic interactions. As depicted in Figures 16 and 17, hyperconjugation of the $\sigma_{C\text{-}C}$ bond with the LUMO of the enone moiety of the dienophile in Figure 16 should stabilize the shallow boat conformation because of the electron-donating nature of a methyl group. On the other hand, hyperconjugation of the $\sigma_{C\text{-}C}$ bond with the LUMO in Figure 17 destabilizes the conformation due to the electron-withdrawing ability of an ester group. The transition state involving the conformation in Figure 16 is therefore expected to be more stable than that involving the conformation in Figure 17. As a result, the addition occurred from the C_4 ester face.

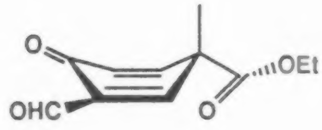


Figure 15

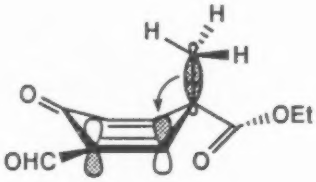


Figure 16

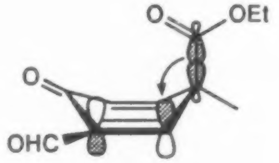


Figure 17

Another factor that could affect the stereochemical outcome of addition of diene to dienone ester **114** is the secondary orbital interaction of the approaching diene with the ester carbonyl group. This type of interaction also requires dienophile **114** to be in a shallow boat conformation with the ester group in a quasi-equatorial position. As such the ester carbonyl group can be coplanar or near coplanar with the cyclohexadienone ring. As depicted in Figure 18, the interaction of the HOMO of the diene and antisymmetric π^* of the ester carbonyl (dashed line) is expected to stabilize the *endo*-to-enone transition state, and as a result, predominate ester face attack was observed. To prove or disapprove this possibility, a model study was then carried out. It was assumed that in the spiro compound **138**, the carbonyl group of the lactone moiety would be sterically confined to be perpendicular instead of being coplanar to the cyclohexadienone ring. In this instance the prerequisite for the proposed secondary orbital interactions would be eliminated. Consequently, the addition of diene to **138** would be subjected to steric interactions of the approaching diene with the lactone carbonyl group or the methylene hydrogens as shown in Figures 19 and 20, respectively.

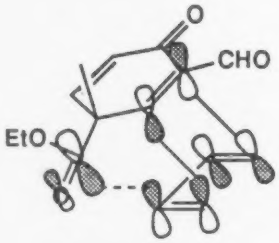
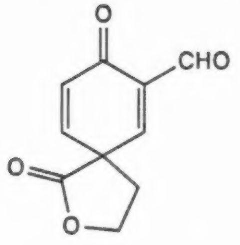


Figure 18



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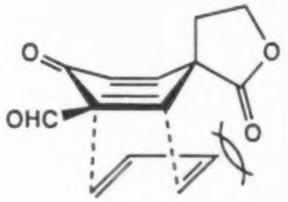


Figure 19

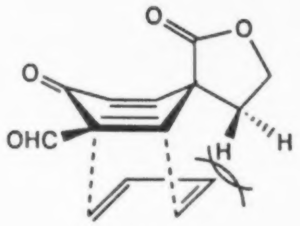
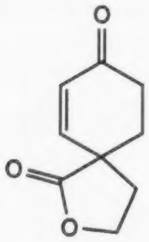


Figure 20

To prepare compound **138**, enone lactone **139** was chosen as the starting material as it has been prepared previously by Danishefsky and coworkers.[168] However, formylation of **139** using the same procedure described previously resulted in exclusive formation of compound **140** without traces of the desired product **141**. The ir spectrum of compound **140** showed carbonyl absorptions at 1727 (C=O, ester), 1662 (C=O, enone) and 1597 cm^{-1} (C=C, enol). The mass spectrum had a molecular ion peak at m/z 240.1002 corresponding to the formula $C_{12}H_{16}O_5$. In the ^1H nmr spectrum, the chelated enol proton was at δ 13.60 as a broad singlet. The vinylic proton was at δ 7.49, also as a broad singlet. The ring juncture proton at δ 4.48 (dd, J = 4.5, 3.5 Hz) was obviously at the equatorial position as indicated by the coupling patterns. Therefore, the ring juncture must be *cis* since it is sterically impossible otherwise. To avoid the problem of lactone ring opening, the trace amount of ethanol in ethyl formate was removed by distillation over calcium hydride. It was found however that the formylation reaction did not take place without the catalysis of ethanol. The use of LDA as a base was also studied. It was observed that the reaction did not proceed at -78°C. At 0°C the reaction mixture decomposed as indicated by TLC analysis.



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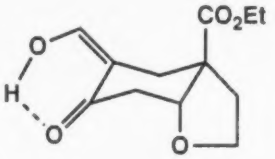
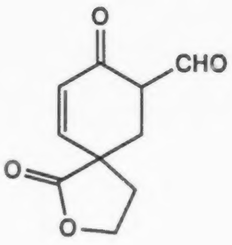
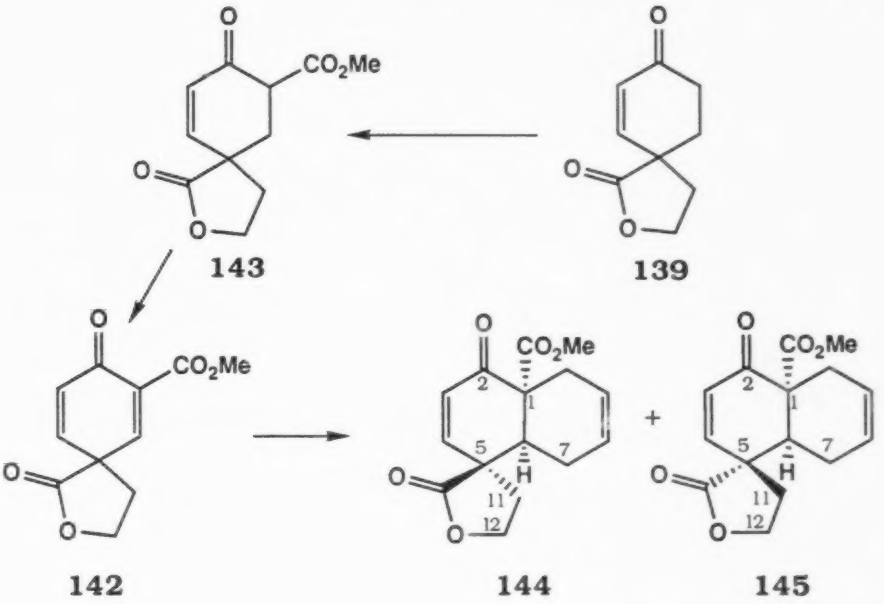


140



141

Compound **142** was then chosen for the model study. Acylation of **139** using Mander's reagent gave keto ester **143** in 90% yield as a mixture of two isomers since two sets of signals were observed in the ^{1}H nmr spectrum. The mass spectrum showed a molecular ion peak at m/z 224.0687, in agreement with the formula $C_{11}H_{12}O_5$. Dehydrogenation of **143** *via* the corresponding phenylselenide afforded the spiro dienone lactone **142**. The ir spectrum of compound **142** showed carbonyl absorptions at 1768 (C=O, lactone), 1741 (C=O, ester) and 1669 cm^{-1} (C=O, enone). In the ^{1}H nmr spectrum, three vinylic protons appeared at δ 7.50 (d, J = 3 Hz), 6.82 (dd, J = 10, 3 Hz) and 6.53 (d, J = 10 Hz). The singlet at δ 3.86 was attributed to the methoxy group. The ethylene unit in the lactone moiety was indicated by the signals at δ 4.62 (m) and 2.67 (m). The mass spectrum did not give the molecular ion peak. Instead, a peak appeared at m/z 191.0346 corresponding to the formula $C_{10}H_7O_4$ due to the loss of a methoxide ion from the molecular ion. Peaks were also observed at m/z 147.0448 [$C_9H_7O_2$, (M-COOMe)$^+$], 120.0576 [base peak, C_8H_8, (M-COOMe and COO)$^+$]. In the chemical ionization mass spectrum, the peak at m/z 240 corresponded to the $[M+NH_4]^+$.



When lactone **142** was reacted with 1,3-butadiene at room temperature using zinc chloride as a catalyst, two adducts were formed in 45:55 ratio in a combined yield of 85% along with 10% recovered starting material. The two compounds were readily separated by flash chromatography or by recrystallization from dichloromethane and pentane. The less polar minor product had a melting point of 160-161°C. The mass spectrum displayed a molecular ion peak at m/z 276.0997 corresponding to the formula $C_{15}H_{16}O_5$. In the ir spectrum, three carbonyl bands were observed at 1768 (C=O, lactone), 1728 (C=O, ester) and 1692 cm^{-1} (C=O, enone). In the ^{1}H nmr spectrum, four vinylic protons appeared at δ 6.45 (dd, J = 10, 2 Hz), 6.24 (d, J = 10 Hz), 5.68 (m) and 5.56 (m). The signal at δ 3.13 (ddd, J = 9, 7, 2 Hz) was attributed to the ring juncture proton. In the ^{13}C APT nmr spectrum, a total of 15 signals were observed. Three carbonyl carbons appeared at δ 193.39, 175.82 and 174.23. Four signals at δ 144.32, 129.99, 123.57 and 123.43 indicated the presence of two double bonds. The methoxy carbon was at δ 53.00 and the angular carbon appeared at δ 38.15.

The more polar major compound was a hexagonal crystal with a melting point of 235-236.5°C. The mass spectrum showed a molecular ion peak at m/z 276.0996 indicating the formula $C_{15}H_{16}O_5$. In the ir spectrum, three carbonyl absorptions appeared at 1753 (C=O, lactone), 1737 (C=O, ester) and 1676 cm^{-1} (C=O, enone). In the ^{1}H nmr spectrum, the vinylic protons of the enone moiety appeared at δ 6.73 (d, J = 10 Hz) and 6.12 (d, J = 10 Hz). Two more vinylic protons were observed at δ 5.83 (m) and 5.71 (m). The methoxy methyl was indicated by the singlet at δ 3.74 and the angular ring juncture proton appeared at δ 3.62 as a broad doublet with a coupling constant of 7 Hz. The ^{13}C APT nmr spectrum showed 15 signals. Three carbonyl signals appeared at δ 195.59, 176.88 and 170.90. Four signals at δ 144.94, 127.31, 125.52 and 124.96 indicated the presence of two double bonds. The signal at δ 52.86 was attributed to the methoxy carbon and the C_6 angular carbon appeared at δ 35.91.

To determine the stereochemistry of these compounds, decoupling and NOE experiments were carried out. The ^1H nmr assignments are summarized in Table 13. For the minor compound, irradiation of the methoxy group at δ 3.72 resulted in a 2.7% enhancement of the H_{11} proton at δ 2.56. Irradiation of the H_6 proton at δ 3.13 resulted in enhancements of the H_{11a} or H_{11b} proton (5.4%), the H_{12} proton (7%), the $H_{7\alpha}$ proton (8.4%) and the $H_{10\alpha}$ proton (6.9%) as summarized in Figure 21. Therefore the minor compound was assigned the structure **144**. For the major compound, irradiation of the methoxy group resulted in no enhancements for any of the protons. Irradiation of the H_6 proton resulted in 5.4% enhancement for the $H_{7\alpha}$ proton (Figure 22). It was therefore assigned to structure **145**.

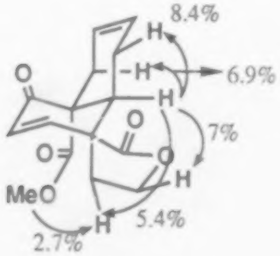


Figure 21

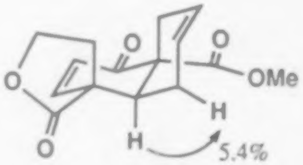


Figure 22

Table 13. ^1H nmr data for adducts **144** and **145**.

144			**145**	
δ (in ppm)	multiplicity (J in Hz)	proton	δ (in ppm)	multiplicity (J in Hz)
6.24	d (10)	H_3	6.12	d (10)

6.45	dd (10, 2)	H_4	6.73	d (10)
3.13	ddd (9, 7, 2)	H_6	3.62	br d (7)
2.39	m	$H_{7\alpha}$	2.31	dm (19)
2.16	m	$H_{7\beta}$	1.75	dm (19)
5.56	dm (10)	H_8	5.71	dm (10)
5.68	dm (10)	H_9	5.83	dm (10)
3.01	dm (17)	$H_{10\alpha}$	2.78	dm (18)
2.29	m	$H_{10\beta}$	2.05	dm (18)
2.56	ddd (13.5, 5, 3)	H_{11a}	2.81	dt (13, 9)
2.33	m	H_{11b}	2.22	ddd (13, 6, 3.5)
4.39-4.45	m (2 H)	H_{12}	4.32-4.44	m (2 H)
3.72	s	OMe	3.74	s

The above results clearly suggest that steric interactions are not the dominant factors in the Diels-Alder reactions of dienophiles such as **114**, **123** and **127**. The spiro lactone model may not serve as a direct proof that secondary orbital interaction is the controlling factor. However, it does demonstrate the importance of coplanarity of the ester carbonyl group in **114** with the cyclohexadienone ring which is the premise for secondary orbital interactions. Furthermore, this model study suggests that subtle changes in structure can impart profound influence on the facial selectivity of Diels-Alder reactions.

This model unfortunately can hardly explain the observed ester face attack by dienes in the *endo* to the α,β-unsaturated aldehyde transition state **116a** where the secondary orbital interaction is spacially too remote. As a result, a third factor, the electrostatic interaction between **114** and the approaching diene which might influence the facial selectivity of Diels-Alder reaction of dienone ester **114** is then considered. The simple electostatic interaction model was originally proposed by Hahn and Hehre[98] to explain the facial selectivity of allylic heterosubstituted dienes or dienophiles. It was stated that cycloaddition of electron rich diene and electron poor dienophile should occur preferentially onto the diene face which was the more nucleophilic and onto the dienophile which exhibited the greater electrophilicity. This simple model has been successfully used to explain numerous observed facial selectivities of Diels-Alder reactions such as the ones listed in Table 1 in the Introduction section. It was also used to explain the observed facial selectivity of allylic heterosubstituted dienophiles[111,176-183] as shown in Table 14. In the case of dienone ester **114**, the more electrophilic face is the ester face as shown in Figure 23. The nucleophilic nature of dienes therefore prefers the addition from the ester face. Not only can this simple model explain the addition of dienes from the ester face *via* the *endo* to enone transition **115a**, but also it can explain the addition of dienes *via* the *endo* to α,β-unsaturated aldehyde transition state **116a**. Furthermore, this model does not conflict with the results observed for the spiro dienone lactone. In this case, the lone pair of electrons of the lactone carbonyl oxygen shields the electron deficient carbon of the lactone carbonyl (Figure 24). As a result, the bottom face in Figure 24 is actually more electron rich than the top face, and the addition from the top face is therefore favored.

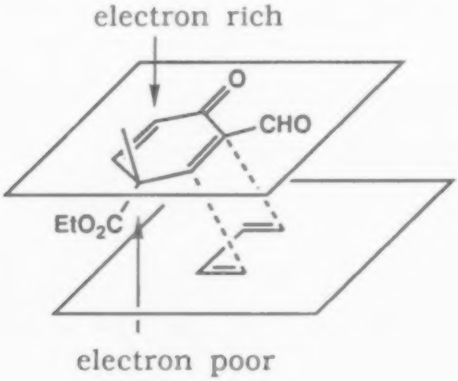

electron rich
O
CHO
EtO2C
electron poor

Figure 23

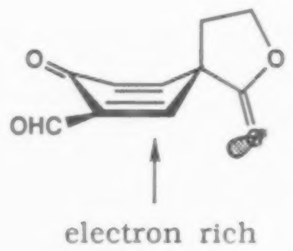
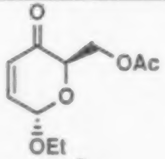
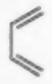
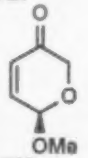
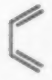
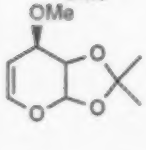
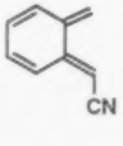
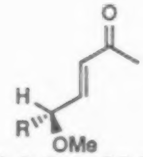
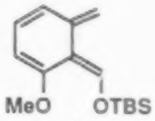
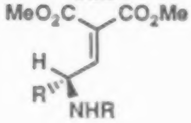
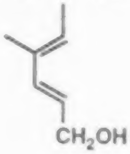
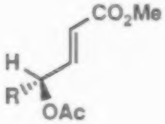
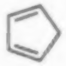
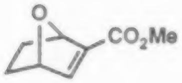
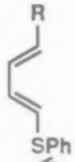
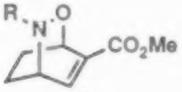
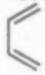
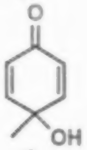
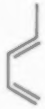
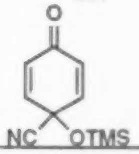
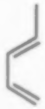

O
OHC
O
O
electron rich

Figure 24

Table 14. Facial selectivity of allylic heterosubstituted dienophiles.

entry	dienophile	diene	selectivity[a]	ref
1			*anti*	176
2			*anti*	177
3			*anti*	178

4			*anti*	179
5			*anti*	180
6			*anti*[b] *syn*	181
7			*syn*	182
8			*syn*	183
9			*syn*	111
10			*anti*	111

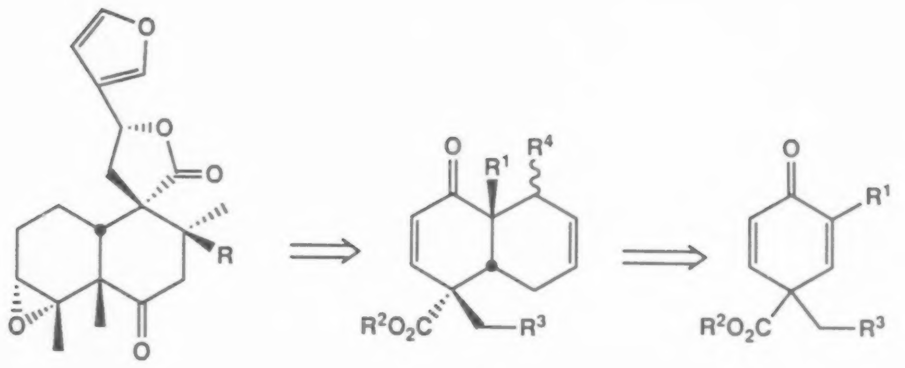
[a] With respect to the heteroatom on the dienophile.

[b] $AlCl_3$ used as a catalyst.

From the above discussions, it is clear that a number of different factors may influence the facial selectivity in these cycloadditions. Although the exact factor or factors responsible for the observed facial diastereoselectivity is still not fully understood, the important factors that must be considered include steric effects, enone conformer population ratio of the dienophile in the transition state, secondary orbital interactions, and electrostatic interactions, etc..

The high degree of facial selectivity observed for compounds **114** and **123** has strong synthetic implications. An extrapolation of the above results suggests that the ester group in compounds of general structure **146** could serve as a directing group for facial selectivity in Diels-Alder reactions. Regardless of the R^3 in **146**, the addition of diene is expected to occur exclusively from the C_4 ester face, resulting in adducts of general structure **147** which can be used as advanced intermediates in the construction of some structurally unique polyoxygenated clerodane diterpenes. Two examples are given below.

3α,4α-Epoxy-6-oxo-15,16-epoxy-8β,10β**H**-*cis*-clerodane-13(10),14-trien-20,12-olide (**148**) is a *cis*-clerodane which has been isolated from P. *eenii* S. Moore by Bohlmann and coworkers.[184] This natural compound can in principle be constructed from **147** as illustrated in the retro-synthetic analysis in Scheme 22.



R = H, OH.
148

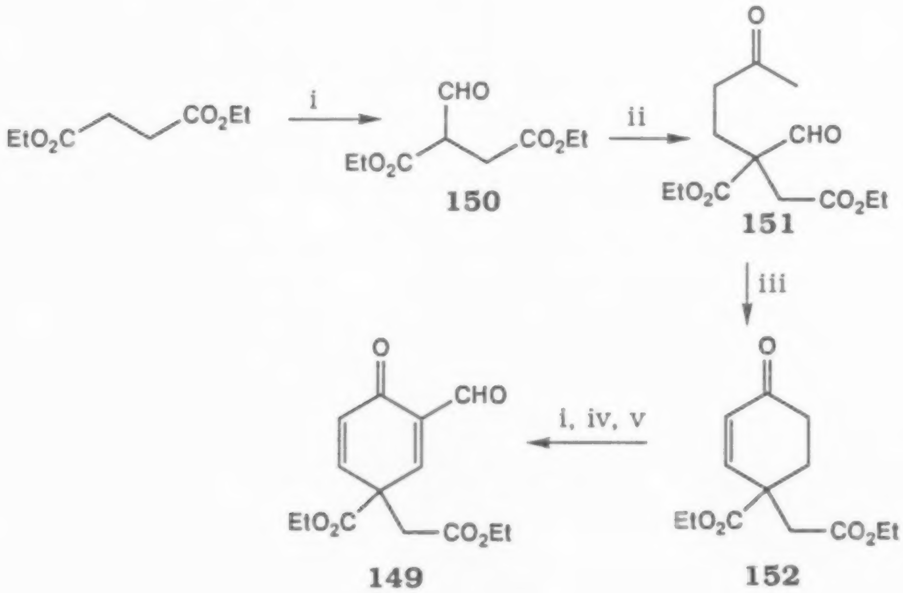
147

146

Scheme 22

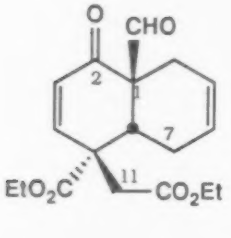
Consequently, dienophile **149** was prepared according to Scheme 23 and its reactions with 1,3-butadiene and *trans*-piperylene were studied. Formylation of diethyl succinate with ethyl formate gave compound **150**. Michael addition of **150** with methyl vinyl ketone using DABCO as base afforded **151**. Intramolecular aldol condensation under acidic conditions with azeotropic removal of water gave dienone ester **152**[152] in 80% overall yield. Subsequent formylation and dehydrogenation gave **149** in 50% yield from **152**. The moderate yield was partially attributed to the relatively high solubility of **149** in water. Compound **149** was a light yellowish crystal with a m.p. of 87-88°C. The ir spectrum of **149** showed carbonyl absorptions at 1736 (C=O, esters), 1708 (C=O, aldehyde) and 1670 cm^{-1} (C=O, enone). In the ^1H nmr spectrum, the formyl proton appeared at δ 10.22. Three vinylic protons were observed at δ 7.81 (d, J = 3 Hz), 7.11 (dd, J = 10, 3 Hz) and 6.47 (d, J = 10 Hz). Two doublets at δ 2.98 and 2.89 with coupling constants of

16.5 Hz each were attributed to the methylene protons adjacent to the ester group. The mass spectrum did not show the molecular ion peak. However, the base peak at m/z 207.0469 corresponding to the formula $C_{11}H_{11}O_4$ was due to the loss of the ethoxycarbonyl fragment from the molecular ion. The chemical ionization mass spectrum showed a peak at m/z 298 for $[M+NH_4]^+$. The elemental analysis also supported the structure assigned.


EtO2C
CO2Et
i
CHO
EtO2C
CO2Et
150
ii
O
CHO
EtO2C
CO2Et
151
iii
O
CHO
EtO2C
CO2Et
149
i, iv, v
O
EtO2C
CO2Et
152

Scheme 23. Reagents. i, NaH, HCO_2Et; ii, MVK, DABCO; iii, *p*-TsOH, benzene; iv, PhSeCl, pyridine; v, H_2O_2.

When dienophile **149** was reacted with 1,3-butadiene using zinc chloride as a catalyst for 18 h at room temperature, virtually one adduct **153** was formed in 85% yield. The mass spectrum showed a molecular ion peak at 334.1420 corresponding to the formula $C_{18}H_{22}O_6$. The ir spectrum displayed carbonyl absorptions at 1732 and 1672 cm^{-1}. In the ^1H nmr spectrum, the singlet at δ 9.61 was attributed to the formyl proton. Four vinylic protons appeared at δ 7.22 (d, J = 10 Hz), 6.10 (d, J = 10 Hz), 5.67 (m) and 5.55 (m). The doublet of doublets at δ 2.86 (J = 7, 3.5 Hz) was attributed to the H_6 angular proton. Two doublets at δ 3.27 (J = 16.5 Hz) and 2.47 (J = 16.5 Hz) were assigned to the methylene protons neighboring ethoxycarbonyl moiety. The $H_{10\beta}$ and $H_{10\alpha}$ protons appeared at δ 2.68 (d quintet, J = 18, 2.8 Hz) and 2.47 (dm, J = 18), respectively. The $H_{7\alpha}$ and $H_{7\beta}$ protons appeared at δ 2.41 (dm, J = 19 Hz) and 2.10 (dm, J =19 Hz). In the ^{13}C APT spectrum, a total of 18 signals were observed. Ten signals were in-phase and the rest were anti-phase with respect to the $CDCl_3$ signal. The formyl carbon was at δ 200.67. Three more carbonyl carbons appeared at δ 197.13, 171.28 and 170.20. Four signals at δ 148.95, 127.45, 125.24 and 123.03 indicated the presence of two double bonds. Attempts to confirm the stereochemistry of **153** by NOE experiments were not very successful. Irradiation of the doublet at δ 3.17 resulted in 48% enhancement for the doublet at δ 2.47 and 4.4% enhancement for the H_6 angular proton at δ 2.86 (Figure 25). Only about 0.5% enhancement was observed for the formyl proton, which was not conclusive for the stereochemistry. However, the structure was indirectly confirmed as will be discussed later on.



153

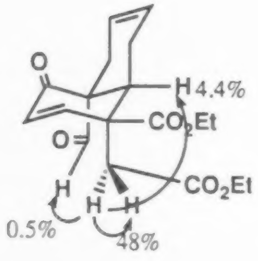
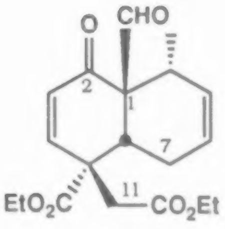


Figure 25

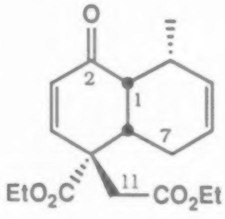
The reaction of compound **149** with *trans*-piperylene was much fasterthan that with 1,3-butadiene. The reaction was finished in 3 h at 0°C under zinc chloride catalysis, affording adduct **154** as the exclusive product in 85% yield. The mass spectrum of **154** showed a molecular ion peak at m/z 348.1576 corresponding to the formula $C_{19}H_{24}O_6$. The ir spectrum displayed carbonyl absorptions at 1737 and 1691 cm^{-1}. In the ^1H nmr spectrum, the formyl proton was at δ 9.69. Four vinylic protons appeared at δ 7.09 (dd, J = 10.5 , 2 Hz), 6.05 (d, J = 10.5 Hz), 5.58 (ddd, J = 10, 2, 2 Hz) and 5.49 (ddd, J = 10, 3.5, 3 Hz). The signal at δ 2.96 (ddd, J = 9, 7, 2 Hz) was attributed to the H_6 angular proton. Two doublets at δ 3.10 (J = 16.5 Hz) and 2.64 (J = 16.5 Hz) were attributed to the methylene protons adjacent to the carbethoxy moiety. The multiplet at δ 2.74 corresponded to the H_{10} proton. The C_{10} methyl group appeared at δ 1.28 as a doublet with a coupling constant of 7 Hz. In the ^{13}C APT nmr spectrum, a total of 19 signals were observed. Nine signals were in-phase and the rest were anti-phase with the $CDCl_3$ signal. The formyl carbon appeared at δ 201.30. Three signals at δ 196.01, 172.02 and 169.79 were attributed to the enone carbonyl carbon and the two ester carbonyl carbons. Four signals at δ 145.31, 129.55, 129.19 and 123.35 indicated the presence of two double bonds.

The stereochemistry of adduct **154** was confirmed by a combination of chemical transformations and spectroscopic methods. Deformylation of **154** in ethanol in the presence of a trace amount of sodium ethoxide gave compound **155** as the exclusive product. Recrystallization of **155** from ethanol and water gave a needle like crystal with m.p. of 84.5-86.5°C. The mass spectrum of **155** had a molecular ion peak at m/z 320.1620 corresponding to the formula $C_{18}H_{24}O_5$. In the ir spectrum, two carbonyl absorption bands appeared at 1735 and 1690 cm^{-1}. In the ^1H nmr spectrum, the signal for the formyl proton of the starting material disappeared. Four vinylic protons were at δ 7.01 (dd, *J* = 10, 2 Hz), 5.89 (d, *J* = 10 Hz), 5.58 (dm, *J* = 10 Hz) and 5.44 (dm, 10 Hz). In the ^{13}C APT nmr spectrum, a total of 18 signals were observed. Three carbonyl carbons appeared at δ 198.88, 172.80 and 170.36. Four signals at δ 144.49, 131.86, 129.25 and 123.18 indicated the presence of two double bonds.

To determine the stereochemistry of compound **155**, extensive ^1H decoupling experiments were carried out. The ^1H nmr data are summarized in Table 15. From the coupling pattern of the H_1 proton at δ 2.85 (ddd, *J* = 3.5, 3.5, 0.5 Hz), a *cis* ring juncture could be assigned since no coupling larger than 3.5 Hz was observed. This assignment was supported by the long range W-couplings for H_1-H_9 (0.5 Hz) and H_4-H_6 (2 Hz). The complete stereochemistry was determined with the assistance of the NOE experiments. Irradiation of the H_1 proton resulted in 15.8% enhancement for the doublet at δ 3.02 (H_{11a}), 8% enhancement for the H_6 proton and 12.5% enhancement for the H_{10} proton (Figure 26). Further irradiation of H_{10} at δ 2.43 resulted a 8.3% enhancement for H_6 suggesting a *cis* relationship of the two protons. These results not only confirmed the *cis* ring juncture for **155**, but also the stereochemistry at C_5 and C_{10}. The structure of compound **155** was further confirmed by the single crystal X-ray crystallography analysis. The preliminary results are shown in Figure 26. The establishment of the stereochemistry for **155** also indirectly confirmed the structure assigned for compound **153**.



154



155

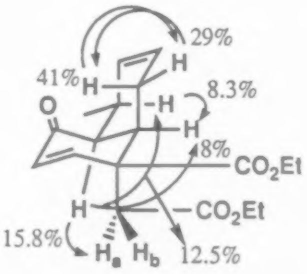


Figure 26

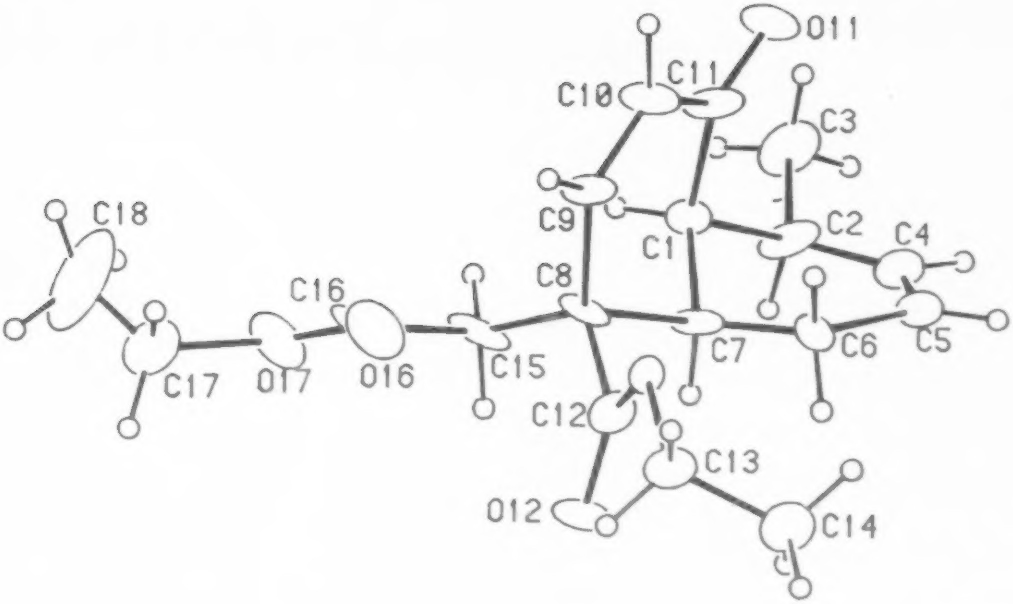
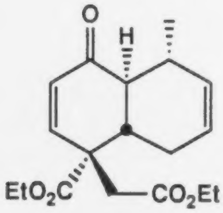

O11
C10
C11
C3
C9
C1
C2
C4
C18
C16
C8
C17
O17
O16
C15
C7
C6
C5
C12
C13
O12
C14

Figure 27. X-ray structure of compound **155**

Table 15. ^{1}H nmr data for compound **155**.

proton	δ (in ppm)	multiplicity (*J* in Hz)
H_1	2.85	ddd (3.5, 3.5, 0.5)
H_3	5.89	d (10.5)
H_4	7.01	dd (10.5, 2)
H_6	2.53	dddd (12, 6, 3.5, 2)
$H_{7\alpha}$	1.81	dm (18)
$H_{7\beta}$	2.08	dddd (18, 12, 4, 2)
H_8	5.44	dm (10)
H_9	5.59	dm (10)
H_{10}	2.43	m
H_{11a}	3.02	d (16)
H_{11b}	3.20	d (16)
C_{10} methyl	1.42	d (7.5)

Interestingly, when attempts were made to convert the aldehyde moiety in **154** into the thioacetal derivative using 1,2-ethanedithiol and $BF_3 \cdot OEt_2$, two inseparable deformylation products were formed in a ratio of 1.4:1. The ^{1}H nmr spectrum of the minor product was identical to that of compound **155**. The major compound was then assigned to the *trans* isomer **156**. Treatment of the mixture with a trace amount of sodium ethoxide in ethanol gave compound **155** exclusively. It appears that compound **155** is the thermodynamically more stable one. This is somewhat surprising since the *trans* isomer with the C_{10} methyl and the C_5 acetate chain in equatorial positions is expected to be the more stable one. The unexpected stability of **155** is probably due to the strong preference for the ester group at C_5 to adapt an equatorial position to avoid unfavorable electronic interactions. As depicted in Figures 28 and 29, the *cis* isomer (Figure 28) can avoid the unfavorable σ_{CC}-π^*_{3-4} interaction while the *trans* isomer (Figure 29) can not. This electronic effect overrides the unfavorable steric interactions encountered in the *cis* isomer. As a result, the *cis* compound is more stable.



156

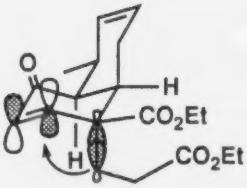


Figure 28

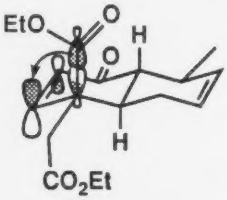
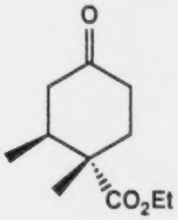


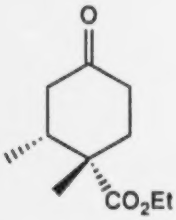
Figure 29

The aforementioned phenomenon seems to be general for 2-cyclohexenone derivatives possessing C_4 carbonyl substituents such as compound **90**. If this is true, then the carbonyl group at the C_4 position of **90** can be used as a directing group to achieve high degree of selectivity in reactions such as hydrogenation, 1,4-

addition reaction and Diels-Alder cycloaddition, etc.. To test the validity of this speculation, a hydrogenation was carried out for enone ester **90**. It was observed that an inseparable mixture of two isomers was obtained in a ratio of 12-10:1 in a combined yield of 86-90%. The ir spectrum of the mixture showed a carbonyl absorption at 1719 cm^{-1}. In the mass spectrum, the molecular ion peak appeared at m/z 198.1250 corresponding to the formula $C_{11}H_{18}O_3$. In the ^1H nmr spectrum, the C_4 methyl group of both compounds appeared at δ 1.36. The C_3 methyl for the major compound appeared at δ 1.03 (d, J = 7 Hz), while the C_3 methyl for the minor compound was observed at a somewhat higher field δ 0.92 (d, J = 7 Hz). The major compound was tentatively assigned to structure **157** and the minor compound was assigned to structure **158**. Attempts to confirm the structural assignment by NOE studies were not successful. As a result, the stereochemistry of **157** remains to be vigorously determined.



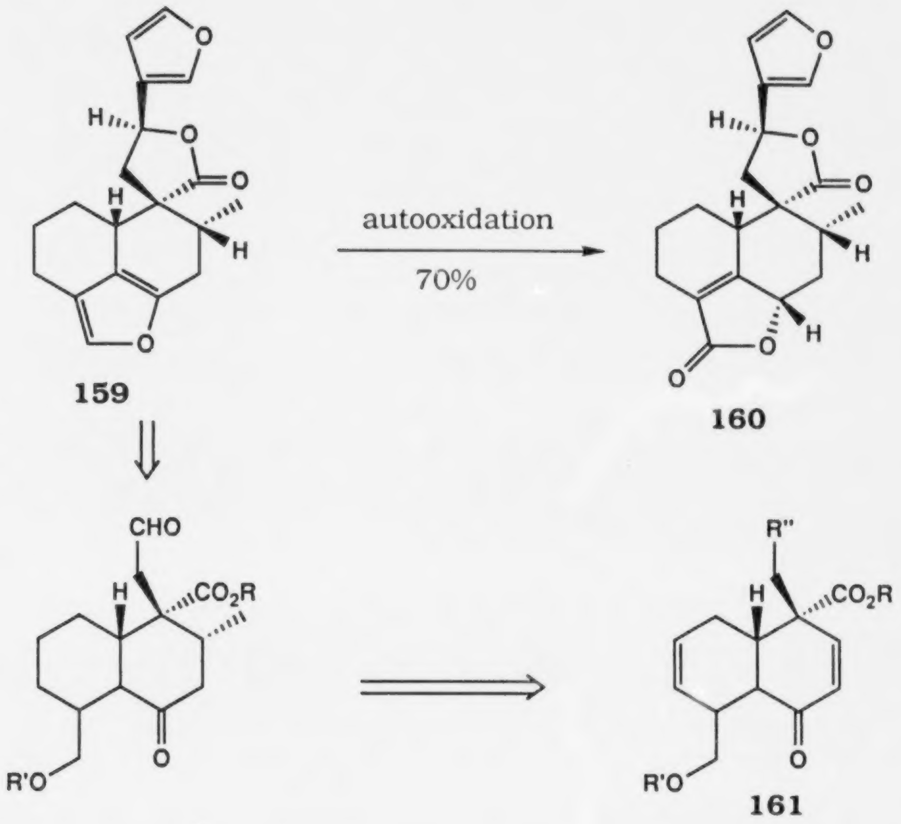
157



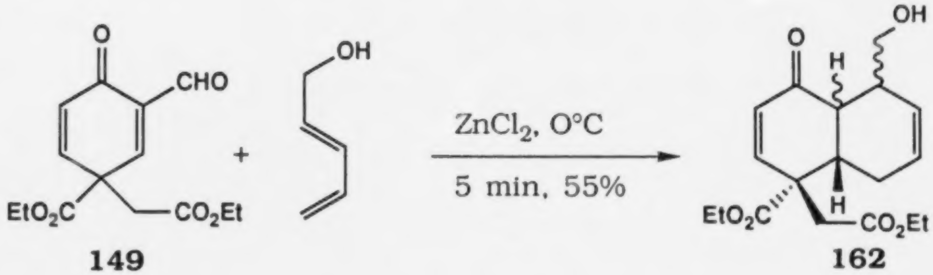
158

The Diels-Alder adduct **154** possesses the three stereogenic centers at C_1, C_5 and C_6 required for the construction of the natural product **148**. Further elaborations towards **148** will be the subject of future research.

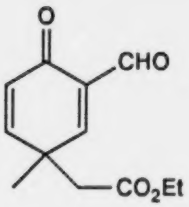
As another example, the possible use of adducts such as **147** as potential intermediates towards the synthesis of maintanin A (**159**)[185] and teucvin (**160**),[186] diterpenes of the *nor*-clerodane family. A retrosynthetic analysis (Scheme 24) suggests a intermediate **161** which can be constructed *via* the Diels-Alder reaction of dienophile **149** and a 5-oxygenated 1,3-pentadiene. The Diels-Alder reaction of dienophile **149** with 5-hydroxy-1,3-pentadiene was thus studied. When the reaction was carried out at 0°C under argon using zinc chloride as a catalyst, one major compound **162** was formed in 55% yield after 5 min. The product was contaminated with ca. 10% of another isomer. The ir spectrum of **162** showed a hydroxy absorption at 3420 along with two carbonyl absorptions at 1730 and 1679 cm^{-1}. The molecular ion peak in the mass spectrum was at m/z 336.3569 corresponding to the formula $C_{18}H_{24}O_6$. In the ^1H nmr spectrum, no formyl proton was observed. Four vinylic protons appeared at δ 7.15 (dd, J = 10, 2 Hz), 5.94 (d, J = 10 Hz), 5.83 (ddd, J = 10, 4, 2 Hz) and 5.41 (ddd, J = 10, 6, 3 Hz). The stereochemistry of **162** remains to be vigorously determined. Further elaboration of **162** toward montanin A and teucvin remins to be carried out.


autooxidation
70%
159
160
CHO
CO$_2$R
R'O
R''
161

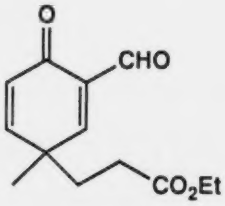
Scheme 24


CHO
EtO$_2$C
CO$_2$Et
149
OH
ZnCl$_2$, O°C
5 min, 55%
162

In order to gain further informations about the influence of an ester group on the facial selectivity in Diels-Alder reactions concerning dienophiles of general structure **39**, dienone ester **163** and **164** were prepared and their Diels-Alder cycloadditions with dienes under zinc chloride catalysis were studied.

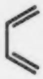
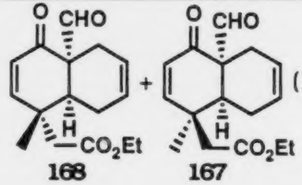
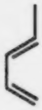
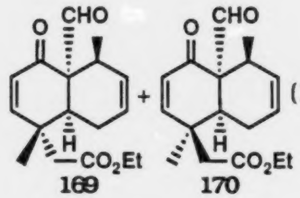
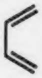
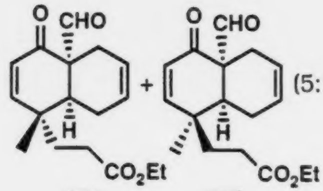


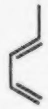
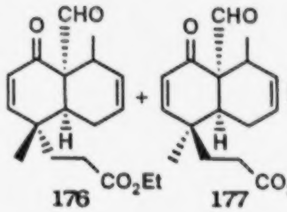
163



164

Table 16. Diels-Alder reactions of dienophiles **163** and **164**.

entry	dieno-phile	diene	catalyst	temp (°C)	time (h)	yield (%)[a]	product (ratio)
1	**163**		$ZnCl_2$	24	72	90	 **168** + **167** (1.7:1)
2	**163**		$ZnCl_2$	24	14	90	 **169** + **170** (1.2:1)
3	**164**		$ZnCl_2$	24	60	76[b]	 **174** + **175** (5:1)

4	**164**		-------	78	42	25[c]	 **176** + **177** (2.2:1)

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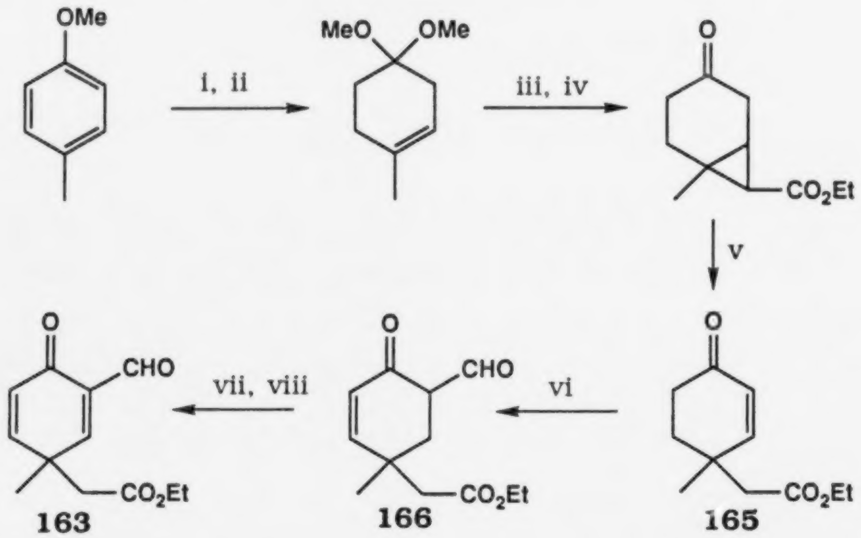
[a] Isolated yield based on starting material used.

[b] The starting material was recovered in 20%

[c] The starting material was recovered in 70%.

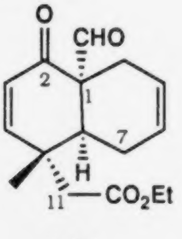
Dienone ester **163** was prepared from enone ester **165**, which in turn was synthesized by a modified literature procedure[187] as shown in Scheme 25. When **165** was reacted with ethyl formate and sodium hydride, enone aldehyde **166** was formed quantitatively. Subsequent phenylselenenylation-oxidative elimination afforded dienone ester **163**. The ir spectrum of **163** showed carbonyl absorptions at 1732 (C=O, ester), 1705 (C=O, aldehyde) and 1666 cm^{-1} (C=O, enone). In the ^1H nmr spectrum, three vinylic protons appeared at δ 7.68 (d, J = 3 Hz), 6.98 (dd, J = 10, 3 Hz) and 6.35 (d, J = 10 Hz). Two doublets at δ 2.71 and 2.65 with coupling constants of 14 Hz each were attributed to the methylene protons adjacent to the ester group. The methyl group appeared at δ 1.41 as a sharp singlet. Signals at δ 4.08 (q, J = 7 Hz) and 1.19 (t, J = 7 Hz) corresponded to the ethoxy group. The mass spectrum did not show the molecular ion peak. However, the peak at m/z 207.0344 corresponding to the formula $C_{11}H_{11}O_4$ was attributed to the loss of a methyl group from the molecular ion. The base peak was at m/z

135.0447 ($C_8H_7O_2$), resulting from the elimination of the ethoxy group from the molecular ion. The elemental analysis was also in support of the structure assigned.

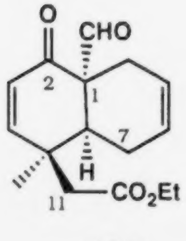


Scheme 25. Reagents. i, Li, liq. NH_3; ii, MeOH, *p*-TsOH; iii, N_2CHCO_2Et, Cu-Zn; iv, *p*-TsOH, acetone; v, ethenol, trace NaOAc; vi, NaH, HCO_2Et; vii, PhSeCl, pyridine; viii, H_2O_2.

Dienone ester **163** reacted with 1,3-butadiene slowly at room temperature under zinc chloride catalysis in dichloromethane, giving two diastereomeric adducts in a ratio of 1.7:1 in a combined yield of 85% along with 10% recovery of the starting material. The mass spectrum of the mixture showed a molecular ion peak at m/z 276.1368 corresponding to the formula $C_{16}H_{20}O_4$. In the ir spectrum, carbonyl absorptions were observed at 1731 (C=O, ester and aldehyde) and 1667 cm^{-1} (C=O, enone). In the ^1H nmr spectrum, two sets of signals were observed. The formyl protons for both compounds were at δ 9.59. The H_6 proton for the major isomer appeared at δ 2.87 as a broad doublet (J = 6 Hz). For the minor isomer, the H_6 proton appeared at δ 2.75 as a doublet of doublets with coupling constants of 7 and 3.5 Hz. The C_5 methyl for the major compound was observed at δ 1.16 while the C_5 methyl for the minor compound was at δ 1.37. The stereochemistry was determined by NOE experiments. Irradiation of the C_5 methyl for the minor isomer at δ 1.37 resulted in a 3.6% enhancement for the formyl proton at δ 9.59 as well as a 15% enhancement for the H_6 proton (Figure 31). Therefore, the minor isomer was assigned to structure **167**, and the major isomer was assigned to structure **168**. This was further confirmed by a NOE experiment on the major compound. Irradiation of the C_5 methyl group at δ 1.16 resulted in no detectable enhancement for the formyl proton. Other enhancements are summarized in Figure 30. The chemical shift difference (0.2 ppm) for the C_5 methyl groups in the ^1H nmr spectrum of adducts **167** and **168** can be attributed to the different environments experienced by these methyls. For **167**, the C_5 is in the deshielding zone of the aldehyde carbonyl group. As a result, it is more downfield shifted than the corresponding methyl of the major isomer **168**.



168



167

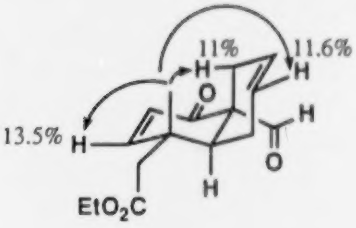


Figure 30

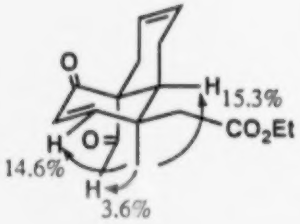
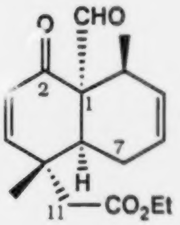
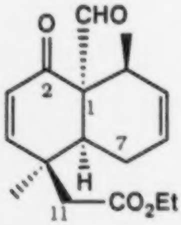


Figure 31

The reaction of dienone ester **165** with *trans*-piperylene in dichloromethane under zinc chloride catalysis was much faster, yielding two isomeric adducts in a ratio of 1.2:1 in 95% yield. The mass spectrum of the mixture showed a molecular ion peak at m/z 290.1518 corresponding to the formula $C_{17}H_{22}O_4$. The ir spectrum displayed carbonyl absorptions at 1729 and 1688 cm^{-1}. In the ^{1}H nmr spectrum, the C_5 methyl group of the major adduct appeared at δ 1.21 while the C_5 methyl of the minor adduct was at δ 1.39. Therefore, the major product was assigned to structure **169** and the minor product was assigned to **170**. Some of the ^{1}H nmr data for these compounds are listed in Table 17. The reactions of **163** with 1,3-butadiene and *trans*-piperylene are compiled in Table 16



169



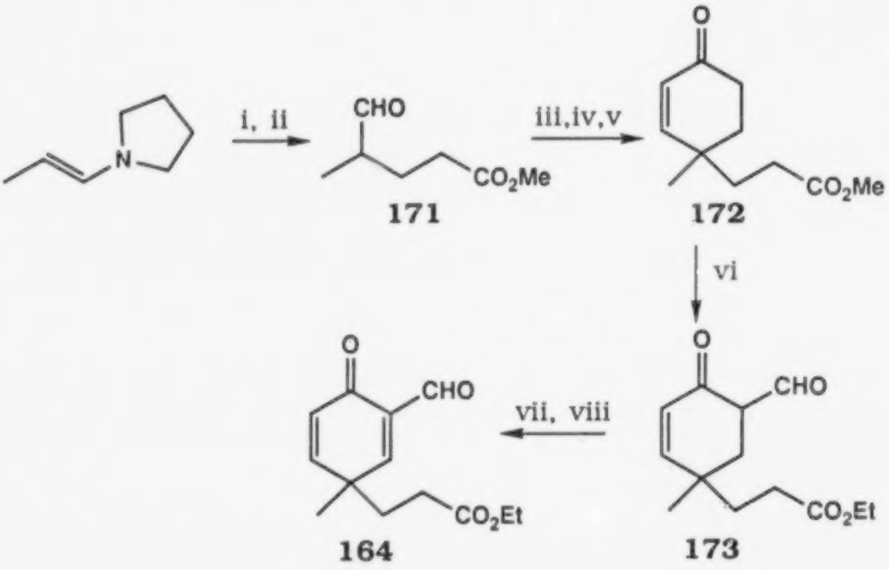
170

Table 17. ^1H nmr data for adducts **169** and **170**.

169			**170**	
δ (in ppm)	multiplicity (*J* in Hz)	proton	δ (in ppm)	multiplicity (*J* in Hz)
9.64	s	Formyl-H	9.62	s
5.99	d (10)	H_3	5.94	d (10)
6.65	d (10)	H_4	6.55	dd (10, 2)
2.99	t (6)	H_6	2.90	m
1.21	s	C_5 Me	1.39	s
1.16	d (7)	C_{10} Me	1.23	d (7)

Dienone ester **164** was prepared according to Scheme 26. Stork-enamine alkylation[188] of propanal with methyl acrylate followed by hydrolysis gave compound **171**. Michael addition of the enamine derived from **171** with methyl vinyl ketone followed by treatment with hydrochloric acid gave enone ester **172**.[189] Formylation of **172** gave enone aldehyde **173**. Subsequent dehydrogenation afforded dienone ester **164**. The ir spectrum of **164** showed carbonyl absorption bands at 1732 (C=O, ester), 1705 (C=O, aldehyde) and 1668 cm^{-1} (C=O, enone). In the ^1H nmr spectrum, the formyl proton appeared at δ 10.22 as a sharp singlet. The doublet at δ 7.52 (J = 3 Hz) was attributed to the H_3 vinylic proton. The conjugated enone protons appeared at δ 6.38 (d, J = 10 Hz) and 6.80 (dd, J = 10, 3 Hz), respectively. The sharp singlet at δ 1.38 was attributed to the C_4 methyl group and signals at δ 4.07 (q,

J = 7 Hz) and 1.22 (t, J = 7 Hz) corresponded to the ethoxy group. In the mass spectrum, a weak molecular ion peak was observed at m/z 236.1045 corresponding to the formula $C_{13}H_{16}O_4$.

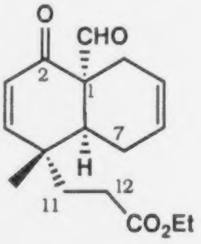


Scheme 26. Reagents. i, CH_2=$CHCO_2Me$; ii, 1 N HCl; iii, pyrrolidine; iv, MVK; v, 2 N HCl; vi, HCO_2Et, NaH; vii, PhSeCl, pyridine; viii, H_2O_2.

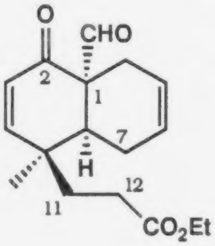
Dienone ester **164** reacted slowly with 1,3-butadiene in dichloromethane at room temperature under zinc chloride catalysis, affording two adducts in a ratio of 5:1 in a combined yield of 76% along with 20% recovery of the starting material. The ir spectrum of the mixture showed carbonyl absorptions at 1732 and 1667 cm^{-1}. The mass spectrum exhibited a molecular ion peak at m/z 290.1513 corresponding to the formula $C_{17}H_{22}O_4$. After careful chromatography, pure samples for each compound were obtained. The ^1H nmr spectrum of the less polar major product

174 resembled that of compound **168**. The formyl proton appeared at δ 9.58. Four vinylic protons were observed at δ 6.63 (d, *J* = 10 Hz), 5.95 (d, *J* = 10 Hz), 5.72 (m, 2 H). The C_5 methyl group appeared at δ 1.10 as a sharp singlet. In the ^{13}C APT nmr spectrum, a total of 17 signals were observed. The formyl carbon appeared at δ 201.30. The other carbonyl carbons were observed at δ 198.89 and 173.09. Four signals at δ 157.34, 127.72, 126.35 and 122.67 indicated the presence of two double bonds. To determine the stereochemistry, an NOE experiment was carried out. Irradiation of the C_5 methyl group at δ 1.10 did not result in any enhancements for the formyl proton and the H_6 angular proton. Instead, enhancements were observed for the H_4 vinylic proton, the H_8 vinylic proton and the $H_{10\beta}$ proton as shown in Figure 32. This not only confirmed that compound **174** was the adduct from the methyl face of dienophile **164**, it also indicated that this compound adopted the conformation as shown.

For the minor more polar product **175**, the formyl proton appeared at δ 9.58. Four vinylic protons appeared at δ 6.65 (d, *J* = 10 Hz), 5.94 (d, *J* = 10 Hz), and 5.72 (br s, 2 H). The doublet of doublets at δ 2.65 (*J* = 7, 4.5 Hz) was attributed to the angular H_6 proton. The C_5 methyl group appeared at δ 1.23 as a sharp singlet. The stereochemistry of **175** was determined by an NOE experiment. Irradiation of the C_5 methyl at δ 1.23 resulted in a 3% enhancement for the formyl proton as well as a 6% enhancement for the H_6 proton (Figure 33). Therefore, the C_5 methyl and the formyl group must be on the same face.



174



175

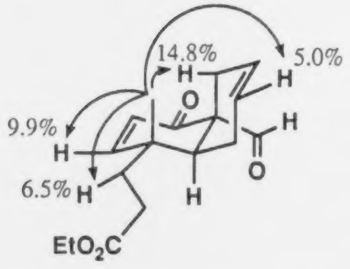


Figure 32

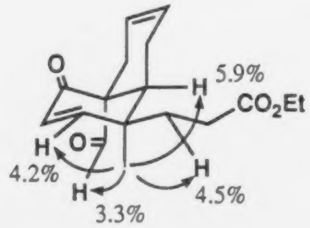
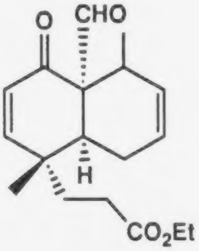
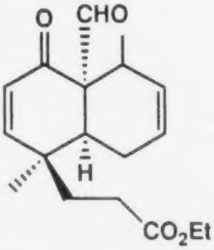


Figure 33

The addition reaction of dienone ester **164** with *trans*-piperylene in refluxing benzene was quite sluggish. Only 30% conversion was observed after 42 h of refluxing, giving rise to an inseparable mixture of four adducts in a ratio of 24:11:2.5:1. The mass spectrum of the mixture showed a molecular ion peak at m/z 304.1670 corresponding to the formula $C_{18}H_{24}O_4$. In the ir spectrum, carbonyl absorptions were observed at 1731 and 1665 cm^{-1}. The ^1H nmr spectrum of the mixture was very complicated. The chemical shifts of the C_5 methyl group for the two major compounds appeared at δ 1.12 and 1.29, respectively. By comparing with the spectral data of compounds **174** and **175**, the two major adducts were tentatively assigned to structures **176** and **177**. These assignments were confirmed by an NOE experiment. Irradiation of the methyl at δ 1.12 resulted in no enhancement for any of the formyl protons. The stereochemistry at C_{10} in each case remaines to be determined. The reactions of **164** with 1,3-butadiene and *trans*-piperylene are also compiled in Table 16.



176

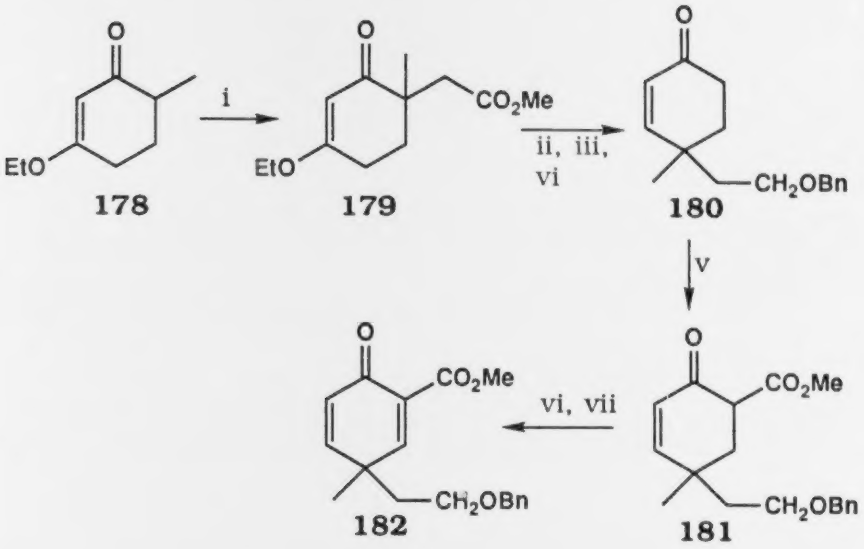


177

An examination of the results obtained for the three homologous dienophiles **114** (Table 5, entries 1-8), **163** (Table 16, entries 1,2) and **164** (Table 16, entries 3,4) reveals a trend that on going from **114** to **164**, the influence of the ester group on the facial selectivity diminishes. In case of dienone ester **114**, the electronic factors may dominate the cycloaddition, resulting in virtually exclusive addition of dienes from the C_4 ester face. In cases of dienone esters **163** and **164**, the addition processes may be dominated by steric factors, resulting in reversal of facial selectivity in favor of the attack of dienes from the C_4 methyls of **163** and **164**.

In principle, compounds **169** and **176** from the reactions of **163** and **164** with *trans*-piperylene are excellent candidates for the construction of *cis*-clerodane diterpenes. In practice, however, these adducts are unstable and difficult to isolate in pure form. Therefore, a more practical dienophile **182** was prepared according to Scheme 27.

Stork-Danheiser alkylation[190] of 3-ethoxy-6-methyl-2-cyclohexenone (**178**) with methyl bromoacetate followed by bulb-to-bulb distillation gave **179**. Without further purification, the crude product was reduced by $LiAlH_4$.[191] The primary hydroxy group in the reduction product was protected with benzyl bromide and sodium hydride followed by dilute acid hydrolysis gave cyclohexenone **180** in 60% overall yield. The ir spectrum of compound **180** showed a carbonyl absorption at 1680 cm^{-1}. In the ^1H nmr spectrum, signals at δ 7.30 (m, 5 H) and 4.49 (s, 2 H) were attributed to the benzyl group. Two doublets at δ 6.65 (J = 10 Hz) and 5.57 (J = 10 Hz) corresponded to the β and α protons of the α,β-unsaturated ketone moiety. The C_4 methyl appeared at δ 1.30 as a sharp singlet. The mass spectrum showed a molecular ion peak at m/z 244.1459 corresponding to the formula $C_{16}H_{20}O_2$. The elemental analysis was in complete agreement with the formula. Carbomethoxylation of **180** with dimethyl carbonate and sodium hydride in refluxing DME gave keto ester **181** as a mixture of three isomers in a ratio of 2:1.4:1 as indicated by the ^1H nmr spectrum.

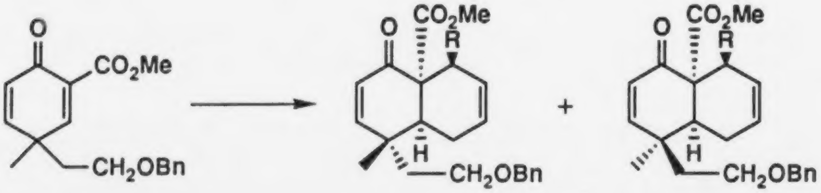


Scheme 27. Reagents. i, *i*-Pr_2NLi, $BrCH_2CO_2Me$; ii, $LiAlH_4$; iii,NaH, BnBr, ; iv, 0.1 N HCl; v, NaH, $(MeO)_2CO$; vi, PhSeCl, pyridine; vii, H_2O_2.

Phenylselenenylation of **181** followed by oxidative elimination afforded dienone ester **182** in 88% yield. The ir spectrum of **182** showed carbonyl absorptions at 1741 and 1664 cm^{-1}. In the ^1H nmr spectrum, the doublet at δ 7.59 (J = 3 Hz) was attributed to the H_3 proton. The vinylic protons of the enone moiety appeared at δ 6.78 (dd, *J* = 10, 3 Hz) and 6.29 (d, *J*= 10 Hz). The singlet at δ 3.80 was attributed to the methoxy group. The C_4 methyl appeared at δ 1.32. The mass spectrum displayed a molecular ion peak at m/z 300.1352. This along with elemental analysis confirmed the required formula $C_{18}H_{20}O_4$.

The Diels-Alder cycloadditions of **182** with *trans*-piperylene and 1,3-butadiene were studied under a variety of conditions. The results are summarized in Table 18.

Table 18. Diels-Alder reactions of dienophile **182**.

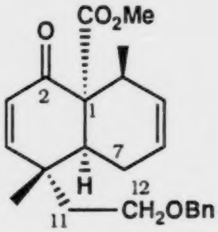


entry	diene	catalyst (eq)	solvent	temp (°C)	time (h)	product ratio	yield (%)[a]
1	R = Me	$ZnCl_2$ (3)	ether	24	17	3.5:1	95
2	R = Me	$ZnCl_2$ (3)	ether	0	24	4:1	95
3	R = Me	$ZnCl_2$ (3)	CH_2Cl_2	0	24	4:1	95
4	R = Me	$ZnCl_2$ (3)	CH_2Cl_2	-20	36	5:1	95
5	R = Me	$FeCl_3$ (2)	CH_2Cl_2	-78-24	1	4:1	85
6	R = Me	$FeCl_3$ (2)	CH_2Cl_2	-55	21	5:1	95
7	R = H	$ZnCl_2$ (3)	CH_2Cl_2	24	13	3:1	31[b]

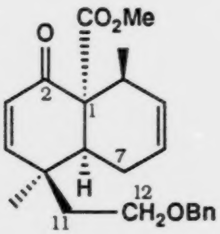
[a] The yields are isolated yields and are based on the starting material used.

[b] The starting material was recovered in 65%.

For *trans*-piperylene, in all cases examined, two adducts **183** and **184** were formed in a ratio of 3.5:1 to 5:1 depending upon the temperature at which the reaction was carried out. It was observed that neither the solvent nor the catalyst used affected the products distribution. The ratio of the products was generally improved by lowering the temperature. However, the improvement was usually fairly small. The yields for these reactions were all excellent except when ferric chloride was used as catalyst at room temperature in which case some decomposition occurred. The two adducts could be readily separated by flash chromatography. For the less polar major compound **183**, the ir spectrum showed carbonyl absorptions at 1725 (C=O, ester) and 1690 cm^{-1} (C=O, enone). In the ^{1}H nmr spectrum, the benzyl moiety was retained as indicated by signals at δ 7.32 (m, 5 H) and two doublets at δ 4.52 (J = 13 Hz) and 4.48 (J = 13 Hz). Signals at δ 6.29 (dd, J = 10, 2 Hz) and 5.91 (d, J = 10 Hz) were attributed to the vinylic protons of the enone moiety. Two more vinylic protons were observed at δ 5.58 (ddd, J = 10, 4, 2 Hz) and 5.50 (ddd, J = 10, 7, 3 Hz). A methoxy group appeared at δ 3.68. Two methyl signals appeared at δ 1.22 (d, J = 7 Hz) and 1.10 (s). In the ^{13}C APT nmr spectrum, a total of 20 signals were observed. Two carbonyl signals appeared at δ 196.50 and 174.54. Seven signals appeared in the region between δ 152.27 and 123.36. From the unusually high intensity of the signal at δ 127.57, it can be concluded that overlaps occurred for the benzene ring carbons. The mass spectrum showed a molecular ion peak at m/z 368.1980 corresponding to the formula $C_{23}H_{28}O_4$. For the more polar minor compound **184**, the ir spectrum showed carbonyl absorptions at 1726 (C=O, ester) and 1689 cm^{-1} (C=O, enone). In the ^{1}H nmr spectrum, The benzyl group appeared at δ 7.31 (m, 5 H) and 4.50 (s, 2 H). Signals at δ 6.29 (dd, J = 10, 2 Hz) and 5.85 (d, J = 10 Hz) were attributed to the vinylic protons of the enone moiety. The other two vinylic protons appeared at δ 5.56 (ddd, J = 10, 4, 2 Hz) and 5.47 (ddd, J = 10, 7, 3 Hz). The sharp singlet at δ 3.71 was attributed to the methoxy group. Two methyl groups appeared at δ 1.26 (d, J = 7 Hz) and 1.15 (s). In the ^{13}C APT nmr spectrum, a total of 21 signals were observed. Two carbonyl carbons appeared at δ 196.23 and 174.65. Eight signals appeared between δ 152.03 and 123.37. The mass spectrum showed a molecular ion peak at m/z 368.1984 corresponding to the formula $C_{23}H_{28}O_4$.



183



184

To determine the stereochemistries of adducts **183** and **184**, extensive ^{1}H decoupling experiments were carried out for both compounds. The data are summarized in Table 19. From the coupling patterns of the H_6 protons for both compounds, it is obvious that both compounds are the *ortho* adducts. To determine the relative stereochemistry at the ring junctures, extensive NOE experiments were carried out for both compounds. For the major compounds, irradiation of the C_5 methyl at δ 1.10 resulted in enhancements for H_4 (15.5%), H_6 (6.9%), $H_{7\alpha}$ (10.2%) and $H_{7\beta}$ (10.2%) (Figure 34). Irradiation of the C_{10} methyl resulted in 17.7% enhancement for the H_{10} proton and 11.8% for the H_9 vinylic proton. Therefore, the structure for the major compound was assigned to **183**.

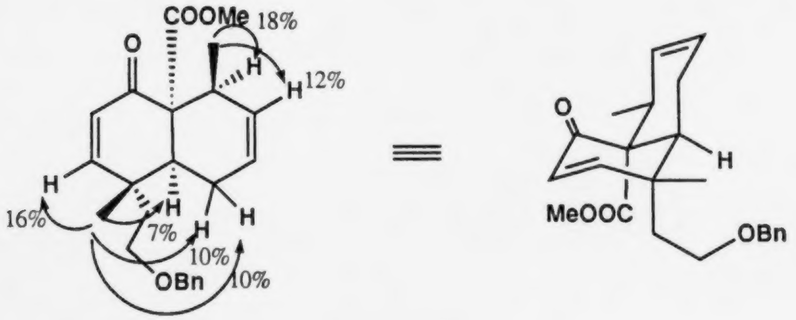


Figure 34

Table 19. ^{1}H nmr data for adducts **183** and **184**.

183			184	
δ (in ppm)	multiplicity (*J* in Hz)	proton	δ (in ppm)	multiplicity (*J* in Hz)
5.92	d (10)	H_3	5.85	d (10)
6.29	dd (10, 2)	H_4	6.29	dd (10, 2)
2.75	ddd (10, 7, 2)	H_6	2.68	ddd (10, 7, 2)
2.16	dm (18)	$H_{7\alpha}$	2.30	dddd (19, 7, 4, 3)
1.95	dm (18)	$H_{7\beta}$	2.02	dm (19)

5.50	ddd (10, 7, 3)	H_8	5.47	ddd (10, 7, 3)
5.57	ddd (10, 4, 2)	H_9	5.56	ddd (10, 4, 2)
2.83	m	H_{10}	2.75	m
1.78	dd (14, 7)	H_{11a}	1.93	ddd (14, 8, 6)
1.72	dd (14, 7)	H_{11b}	1.64	ddd (14, 8, 6)
3.58-3.66	m (2 H)	H_{12}	3.54-3.66	m (2H)
3.69	s	OMe	3.71	s
1.10	s	C_5 Me	1.15	s
1.22	d (7)	C_{10} Me	1.26	d (7)

For the minor compound, irradiation of the C_5 methyl at δ 1.15 resulted in enhancements for the methoxy methyl (2.8%), the H_4 vinylic proton (8.4%) and the H_6 angular proton (10%) (Figure 35). No enhancements were observed for the $H_{7\alpha}$ and $H_{7\beta}$ protons. Irradiation of the C_{10} methyl group resulted in a 27.3% enhancement for H_{10} proton and a 14.1% enhancement for the H_9 vinylic proton. The minor product was therefore assigned to structure **184**. These aforementioned results indirectly confirmed the structural assignment for adduct **109**.

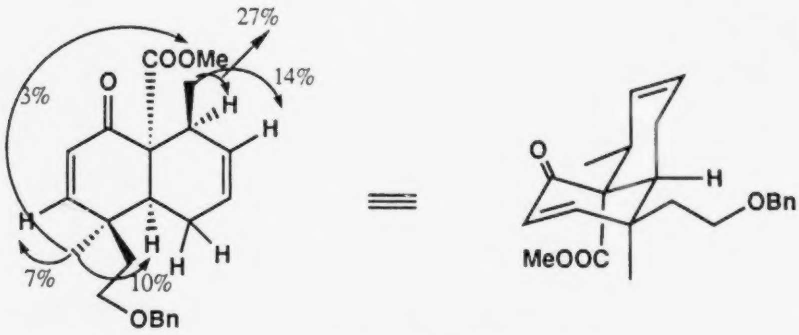
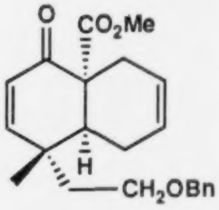
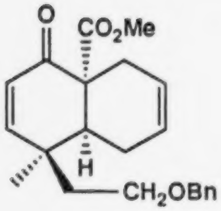


Figure 35

As another example, dienone ester **182** was reacted with 1,3-butadiene. When the reaction was carried out at room temperature for 26 h, a mixture of two inseparable diastereomers (3:1 ratio) were formed in 31% yield along with 65% recovery of the starting material. The mass spectrum of the mixture displayed a molecular ion peak at m/z 354.1830 corresponding to the formula $C_{22}H_{26}O_4$. In the ir spectrum, the mixture displayed carbonyl absorptions at 1742, 1728 and 1673 cm^{-1}. In the ^1H nmr spectrum for the major compound, the C_5 methyl group appeared at δ 1.09 as a sharp singlet. For the minor compound, the C_5 methyl was at δ 1.21. According, the major compound was assigned to structure **185** and the minor compound was assigned to structure **186**. The difference in the chemical shifts (0.12 ppm) can be attributed to the enviroments in which the two methyl groups are situated. For the minor compound **186**, the C_5 methyl is in the deshielding zone of the carbonyl of the angular ester group. As a result, its C_5 methyl is substantially more downfield shifted.

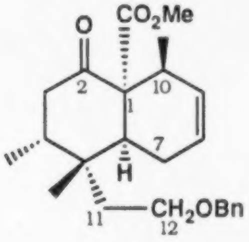


185



186

Adduct **183** was used to carry on the synthesis of *cis*-clerodanes since it possesses the stereochemical features required for the construction of *cis*-clerodane diterpenes. Originally solidagoic acid A (**43**) was chosen as the target molecular as described for adduct **109**. The next phase of the synthesis would involve: (1) introduction of a methyl group at C_4; (2) reduction of the C_2 carbonyl to the saturated hydrocarbon; (3) isomerization of the C_8-C_9 double bond to the C_9-C_{10} position and (4) modification of the side chain. When compound **183** was reacted with 3 equivalents of lithium dimethylcuprate (Me_2CuLi) in ether at 0°C for 1 h, a quantitative yield of the 1,4-addition product **187** was obtained. The ir spectrum of **187** showed an intense carbonyl absorption at 1718 cm^{-1}. In the mass spectrum, the molecular ion peak appeared at m/z 384.2037 corresponding to the formula $C_{24}H_{32}O_4$. In the ^1H nmr spectrum, signals for the vinylic protons of the enone moiety present in the starting material disappeared. A sharp singlet at δ 3.72 was attributed to the methoxy group. Three methyl groups appeared at δ 1.12 (d, J = 7 Hz), 0.95 (s) and 0.89 (d, J = 6.5 Hz). In the ^{13}C APT nmr spectrum, two carbonyl carbons were observed at δ 206.00 and 174.83. Six signals were observed at δ 138.54, 130.28, 128.41, 127.73, 127.60 and 123.01.



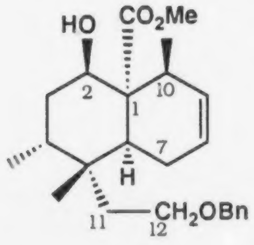
187

To facilitate the assignment of the ^1H nmr spectrum, extensive ^1H decoupling experiments were performed. The data are summarized in Table 20. An NOE experiment was also carried for **187**. Irradiation of the signal at δ 2.52 (H_{10}) resulted in a 5.6% enhancement for the H_6 proton, an 11.5% enhancement for the H_9 vinylic proton and a 4.3% enhancement for the C_{10} methyl. This further confirmed the stereochemistry at C_{10} of compound **187**. The stereochemistry at C_4 could not be determined by decoupling studies. However, tentative assignment could be made by comparing the chemical shifts of the C_4 methyl of compound **187** with those of the C_8 methyls for the naturally occurring compounds. For the *cis*-normal-clerodanes such as solidago lactone V, the C_8 methyl appeared at δ 0.87 which was very close to the value observed for compound **187** (δ 0.89).

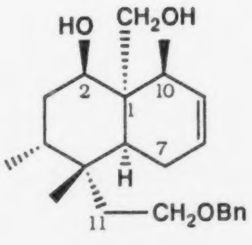
Table 20. ^{1}H nmr data for compound **185**.

proton	δ (in ppm)	multiplicity (J in Hz)
$H_{3\alpha}$	2.14	m
$H_{3\beta}$	2.83	m
H_4	2.15	m
H_6	2.77	dd (10, 7)
$H_{7\alpha}$	2.13	m
$H_{7\beta}$	1.96	m (19, 10, 4, 2)
H_8	5.50	ddd (10, 6, 3)
H_9	5.57	ddd (10, 3, 2)
H_{10}	2.52	m
H_{11}	1.64-1.81 (2 H)	m
H_{12a}	3.73	m
H_{12b}	3.57	ddd (10, 9, 9)
OMe	3.72	s
C_{10} Me	1.12	d (7)
C_5 Me	0.95	s
C_4 Me	0.89	d (6.5)

With compound **187** in hand, the next step of the synthesis involves the selective reduction of the ketone carbonyl group in the presence of the ester group. When compound **187** was reacted with sodium borohydride in methanol at room temperature, no reaction took place even after a prolonged period of time. Only the starting ketone was recovered. The inertness of the ketone carbonyl towards sodium borohydride is probably due to the severe steric hindrance. When Dibal-H was used as the reducing agent in benzene at room temperature, two compounds were formed in approximately 1:1 ratio in 80% yield. The two products could be readily separated by chromatography. For the less polar compound, the ir spectrum showed a hydroxy absorption at 3540 cm^{-1} and a carbonyl absorption at 1702 cm^{-1}. In the ^1H nmr spectrum, the benzyl group was indicated by signals at δ 7.31 (m, 5 H) and 4.48 (s, 2 H). Two vinylic protons appeared at δ 5.56 (ddd, J = 10, 6, 3 Hz) and 5.48 (ddd, J = 10, 4, 2 Hz). The singlet at δ 3.67 was attributed to the methoxy group. Three methyl groups were observed at δ 1.13 (d, J = 7 Hz), 0.85 (s) and 0.83 (d, J = 6.5 Hz). The mass spectrum showed a molecular ion peak at m/z 386.2455 corresponding to the formula $C_{24}H_{34}O_4$. Therefore, this compound was assigned to structure **188**. The stereochemistry at C_2 was not vigorously determined. It was assumed that the delivery of hydride from Dibal-H occurred from the bottom convex face of keto ester **187**.



188



189

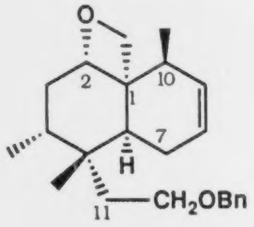
The ir spectrum of the more polar compound displayed a strong hydroxy absorption at 3424 cm^{-1}. No carbonyl absorptions were observed. In the ^1H nmr spectrum, the signals for the benzyl group was retained. The signal for the methoxy group of the starting ketone ester disappeared. Two vinylic protons appeared at δ 5.75 (dm, *J* = 10 Hz) and 5.64 (dm, *J* = 10 Hz). Five protons appeared in the region between δ 3.85 and 3.33. Three methyl groups were observed at δ 1.14 (d, *J* = 7 Hz), 0.89 (s) and 0.82 (d, *J* = 7 Hz). In the ^{13}C APT nmr spectrum, a total of 21 signals were observed. No signals appeared in the carbonyl carbon region. Six signals appeared at δ 137.18, 133.30, 128.55, 128.22, 128.03 and 127.46. The mass spectrum displayed a molecular ion peak at m/z 358.2513 corresponding to the formula $C_{23}H_{34}O_3$. A $[M-18]^+$ peak was also observed. The chemical ionization mass spectrum showed peaks at m/z 376 for $[M+NH_4]^+$ and 359 for $[M+H]^+$. Therefore the more polar product was assigned to diol **189**. To determine the stereochemistry at C_2, extensive ^1H decoupling experiments were carried out for **189**. The ^1H nmr data are summarized in Table 21. Since the H_2 proton overlapped with the H_{12} proton, its coupling constants could not be determined from the decoupling studies. Consequently, compound **189** was transformed into diacetate **190** by reacting with acetic anhydride in pyridine. The mass spectrum of **190** did not give the molecular ion peak. In the chemical ionization mass spectrum, the base peak appeared at m/z 460 corresponding to $[M+NH_4]^+$. In the ^1H nmr spectrum, the broad singlet at δ 4.82 was attributed to the H_2 proton. Two sharp singlets at δ 2.00 and 1.97 indicated the presence of two acetate groups. Interestingly, one of the methyl groups at δ 0.96 was broadened. It was assumed that a fast equilibrium existed between several conformations of **190** at room temperature. From the half width (ca. 8 Hz) of the signal for H_2, it can be concluded that the H_2 proton is probably in an equatorial position. However, this can not be used to assign the stereochemistry at C_2 because of the conformational flexibility of the molecule.

Table 21. ^{1}H nmr data for compound **189**.

proton	δ (in ppm)	multiplicity (*J* in Hz)
H_2	3.60	m
H_{3a}	1.53	dd (8, 3)
H_{3b}	1.53	dd (8, 3)
H_4	2.21	m
H_6	2.33	m
$H_{7\alpha}$	2.37	m
$H_{7\beta}$	2.13	m
H_8	5.76	dm (10)
H_9	5.64	dm (10)
H_{10}	2.83	m
H_{11a}	2.02	ddd (15, 9, 5)
H_{11b}	1.59	ddd (15, 6, 4)
H_{12a}	3.69	ddd (9, 9, 4)

H_{12b}	3.59	m
C**H**HOH	3.85	dd (13, 4)
CH**H**OH	3.33	dd (13, 10)
CHHO**H**	4.32	br d (10)
-O**H**	2.49	br s
C_5 Me	0.89	s
C_4 Me	0.82	d (7)
C_{10} Me	1.14	d (7)

When keto ester **187** was reduced with lithium aluminum hydride in THF at room temperature, two compounds were produced in a ratio of 1:1 in 70% yield. The more polar compound was identical in every respect (TLC, ^{1}H nmr) with diol **189**. The less polar compound was identified as compound **191** by spectroscopic methods. The mass spectrum showed a molecular ion peak at m/z 340.2393 corresponding to formula $C_{23}H_{32}O_4$. The ir spectrum did not display either hydroxy absorptions or carbonyl absorptions. In the ^{1}H nmr spectrum, the benzyl group was retained. Two vinylic protons appeared at δ 5.56 (ddd, J = 10, 6, 3 Hz) and 5.45 (ddd, J = 10 4, 2 Hz). No methoxy group was observed. Five protons appeared in the region between δ 4.18-3.56. Three methyl groups were at δ 1.22 (d, J = 7 Hz), 0.85 (s) and 0.83 (d, J = 7 Hz). In the ^{13}C APT nmr spectrum, a total of 21 signals were observed. No signals appeared in the carbonyl carbon region. Six signals were observed at δ 137.54, 131.75, 128.48, 128.37, 128.06, 127.20 and 123.92 indicated the presence of a benzene ring and a double bond. To facilitate the assignment of the ^{1}H nmr spectrum, ^{1}H decoupling experiments were carried and the data are summarized in Table 22. From the coupling pattern of the H_2 proton (dd, J = 8, 8 Hz), the C-O bond at C_2 was probably axial.



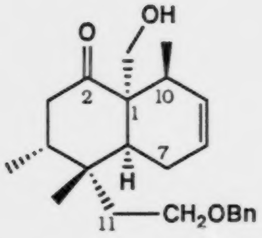
191

Table 22. ^{1}H nmr data for compound **191**.

proton	δ (in ppm)	multiplicity (J in Hz)
H_2	4.02	t (8)
H_{3a} and H_{3b}	1.56	m (2 H)
H_4	1.91	m (8.5, 7)
H_6	2.28	dd (10, 7.5)
H_{7a} and H_{7b}	2.01	m (2 H)
H_8	5.57	ddd (10, 6, 3)
H_9	5.45	ddd (10, 4, 2)
H_{10}	2.74	m
H_{11a}	2.14	ddd (15, 8, 7)
H_{11b}	1.56	m

H_{12a}	3.68	ddd (9, 9, 5.5)
H_{12b}	3.56	ddd (9, 5.5, 5.5)
-C**H**HO-	4.17	d (12)
-CH**H**O-	4.00	d (12)
C_4 Me	0.83	d (7)
C_5 Me	0.85	s
C_{10} Me	1.22	d (7)

Alcohol **188** was potentially useful for the construction of solidagoic acid A. Unfortunately the Dibal-H reduction process was not reproducible. In some instances, only diol **189** was obtained. When the reaction was carried out at -30°C in toluene, similar results were obtained. Attempts were then made to convert the secondary hydroxy group in **188** to the corresponding xanthate. No reaction however took place when **188** was subjected to treatment with sodium hydride and carbon disulfide followed by the addition of methyl iodide at room temperature after a prolonged period of time. Both TLC and ^{1}H nmr spectrum indicated that the starting alcohol was intact. The failure to transform **189** into its corresponding xanthate could again be attributed to steric effects. Diol **189** was a potential candidate for the synthesis of solidagoic acid A. However, the same problem could be foreseen for the secondary hydroxy group as encountered for alcohol **188**. We have therefore developed a better procedure which effected the reduction of the ester group to the primary alcohol level without reducing the ketone functionality. After the 1,4-addition of Me_2CuLi to enone ester **183** at 0°C in ether (the reaction could be monitered by TLC), excess (3-5 eq) of lithium aluminum hydride was then introduced to the reaction mixture in one portion. When the reduction process was finished, ammonium chloride and dilute HCl were added to destroy the excess unreacted lithium aluminum hydride. After flash chromatography, alcohol **192** could be otained in 70% yield consistently. The ir spectrum for **192** showed a hydroxy absorption at 3448 cm^{-1} and a carbonyl absorption at 1692 cm^{-1}. In the ^1H nmr spectrum, two vinylic protons appeared at δ 5.85 and 5.75. Four protons were found between δ 3.58-3.43. Three methyl groups appeared at δ 1.00 (d, J = 7 Hz), 0.97 (s) and 0.89 (d, J = 6 Hz). In the ^{13}C nmr spectrum, a total of 20 signals were observed. A carbonyl carbon appeared at δ 219.94. Five signals appeared at δ 138.30, 132.20, 128.21, 127.65 and 126.60. The mass spectrum did not show the molecular ion peak. In the chemical ionization mass spectrum, the peak at m/z 374 corresponded to $[M+NH_4]^+$. The base peak was at m/z 357 corresponding to $[M+H]^+$. The elemental analysis also supported the structure assigned.



192

To facilitate the assignment of the ^{1}H nmr spectrum, 90° ^{1}H-^{1}H 2D COSY experiments were carried out (Figures 36 and 37). The ^{1}H nmr data are summarized in Table 23.

Table 23. ^{1}H nmr data for compound **192**.

proton	δ (in ppm)	multiplicity (*J* in Hz)
H_{3a}	2.35	dd (16, 10)
H_{3b}	2.14	m
H_4	2.14	m
H_6	2.00	t (7.3)
H_{7a}	2.07	m
H_{7b}	2.14	m
H_8	5.85	dt (10, 4.5)
H_9	5.75	dd (10, 5)
H_{10}	2.50	quintet (7)
H_{11}	1.60	m (2 H)
H_{12a}	3.57	d (11)
H_{12b}	3.45	d (11)

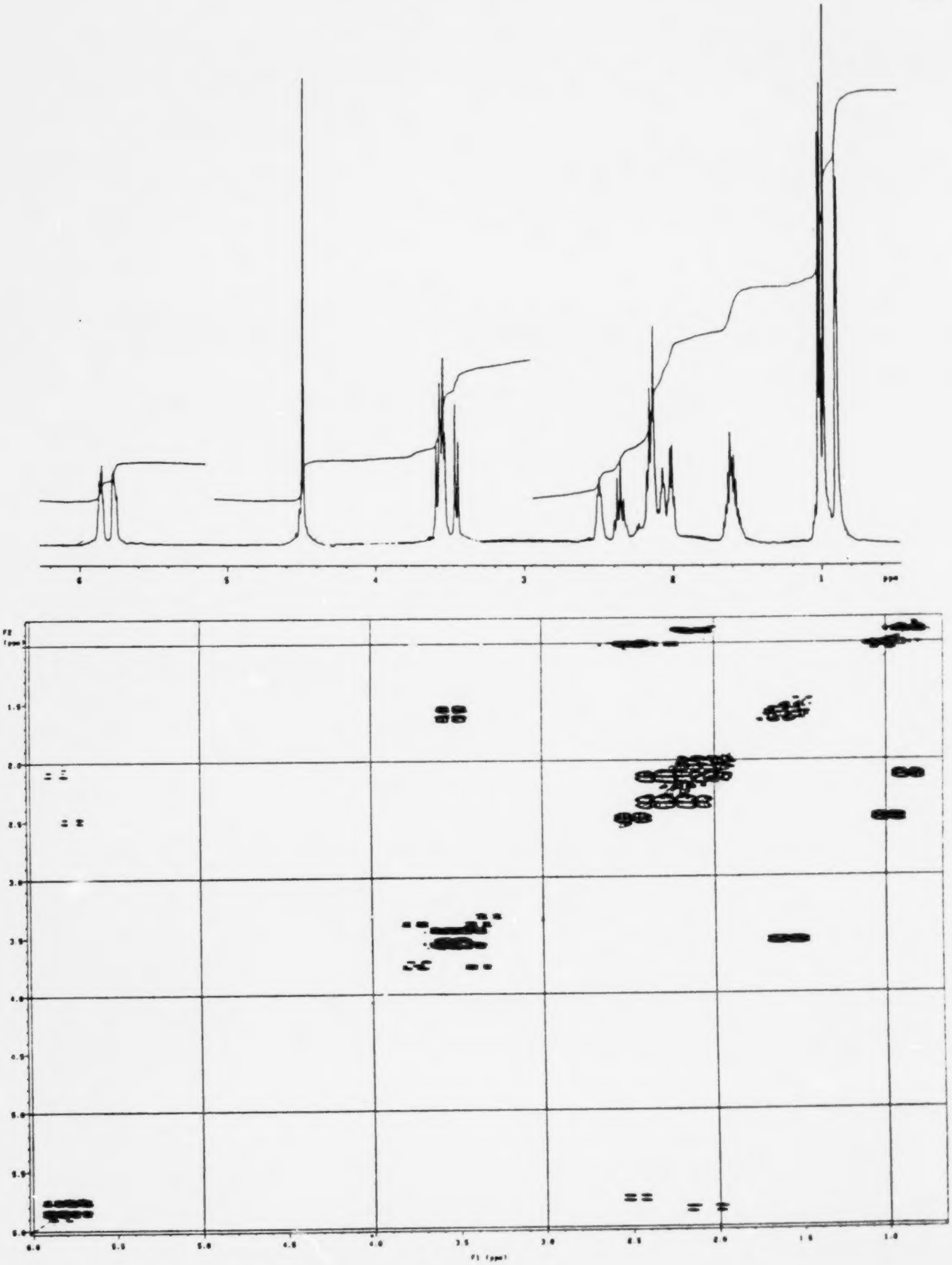


Figure 36. COSY-90 Spectrum of compound **192**.

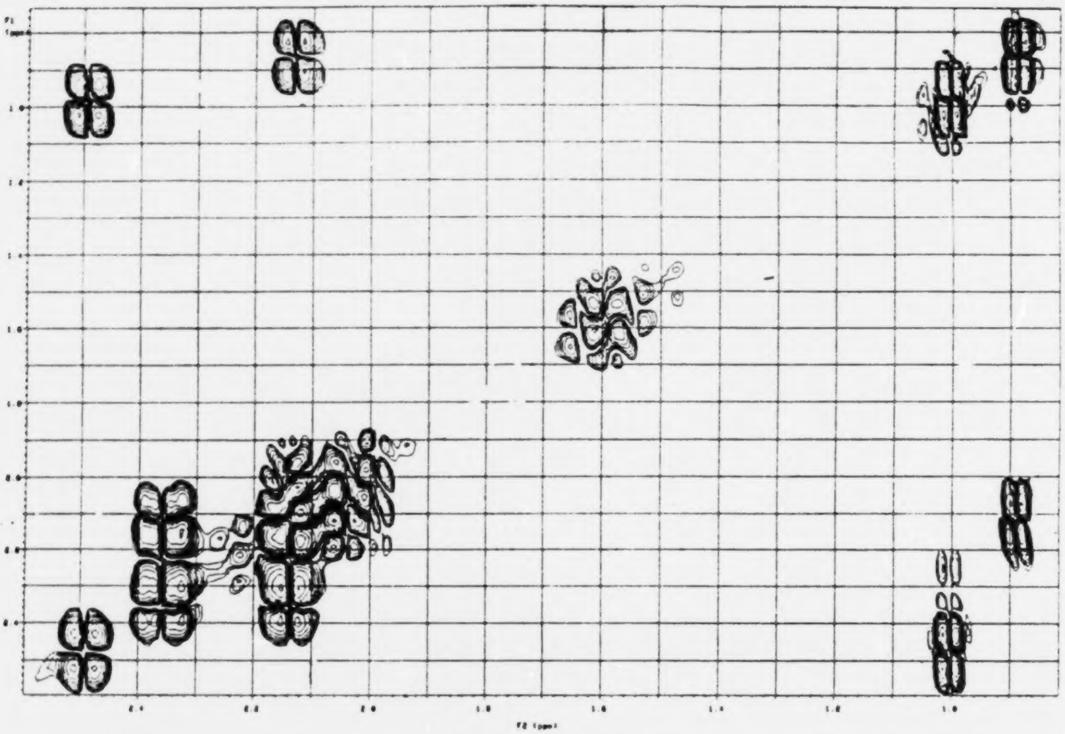
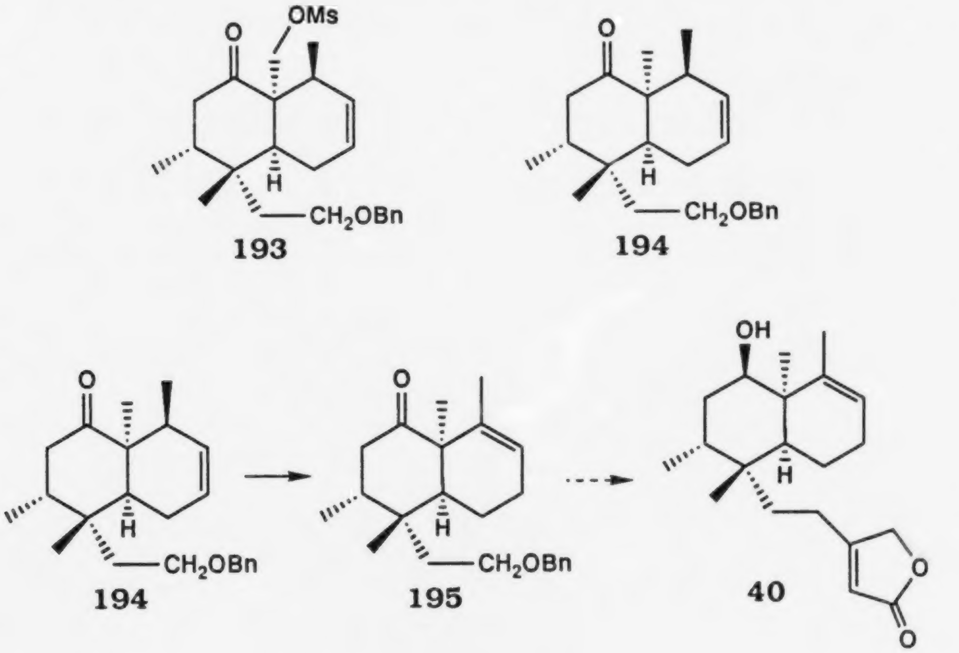


Figure 37. Expansion of COSY-90 Spectrum of compound **192**.

Alcohol **192** was quantitatively transformed into mesylate **193**. When **193** was reduced with zinc metal and sodium iodide in refluxing DMF,[192] compound **194** was obtained in 20% yield along with several unidentified by-products. The ir spectrum for **194** showed a carbonyl absorption at 1703 cm^{-1}. In the ^{1}H nmr spectrum, the benzyl group was retained as indicated by the signals at δ 7.31 (m, 5 H) and 4.50 (s, 2 H). Two vinylic protons appeared at δ 5.85 and 5.75. Four methyl groups were observed at δ 1.24 (s), 0.98 (d, *J* = 7 Hz), 0.96 (s) and 0.89 (d, *J* = 6.5 Hz). The mass spectrum showed a molecular ion peak at m/z 340.2390 corresponding to formula $C_{23}H_{32}O_2$.

Compound **194** possesses all the stereochemical requirements for the construction of solidagolactone IV. As shown in Scheme 28, the next phase of the synthesis requires two key operations: isomerization of the C_8-C_9 double bond to the C_9-C_{10} position (**194** to **195**) and modification of the C_5 side chain to the corresponding one present in the natural occurring compound. These transformations are currently under active investigation.


O
OMs
H
CH₂OBn
193
O
H
CH₂OBn
194
O
H
CH₂OBn
194
O
H
CH₂OBn
195
OH
H
O
O
40

Scheme 28

Experimental

General

Apart from those mentioned in Part 1 of this thesis, the ^{13}C APT spectra were recorded on the Bruker WH-300 (75 MHz) nmr spectrometer. Nuclear Overhauser Enhancement (NOE) experiments were determined in the difference mode in which a control (undecoupled) spectrum was computer subtracted from the irradiated spectrum after Fourier transformation. Positive enhancements are defined as signals possessing an antiphase with respect to the irradiated signal. Samples for NOE measurements were deoxygenated with argon for 10 min prior to use. Two dimensional (2D) homonuclear correlation spectrum (COSY) was performed on the Varian UNITY-500 MHz nmr mechine using the standard proton parameters. Unsatisfactory microanalysis results were obtained for most of the Diels-Alder adducts due to the instability of these compounds.

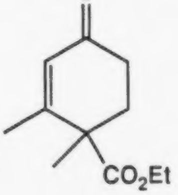
Material

Danishefsky's diene was prepared according to the procedure described by Danishefsky *et al.*[193] 6-Methyl-3-ethoxy-2-cyclohexenone was prepared according to the procedure by Kende *et al.*[194]

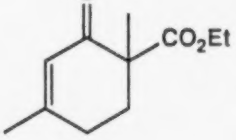
3-Carbethoxy-3-methyl-2,6-heptadione

A mixture of ethyl methylacetoacetate (14.5 g, 0.1 mol), DABCO (17 g, 0.15 mol) and freshly distilled methyl vinyl ketone (MVK) (14 g, 0.20 mol) in THF (or DME) was stirred at room temperature under an argon atmosphere for 3 days and then cooled down to 0°C. Ice-cold 2 N HCl was added to the mixture and the resulting solution was extracted with ether (3 x 100 mL). The extracts were combined, washed with water and brine and dried over magnesium sulfate. After concentration, the residue was distilled at 60-65°C/0.7 torr on a Kugelrohr apparatus to give the product (20.4 g, 95% yield) as a colorless oil: ir (film) 1713 (C=O, ketones and ester); ^{1}H nmr (200 MHz) δ 4.21 (q, J = 7 Hz, 2 H), 2.39-2.50 (m, 2 H), 2.18 (s, 3 H), 2.16 (s, 3 H), 1.99-2.24 (m, 2 H), 1.36 (s, 3 H) and 1.28 (t, J = 7 Hz, 3 H); hrms M^+ 214.1202 (calcd. for $C_{11}H_{18}O_4$: 214.1205).

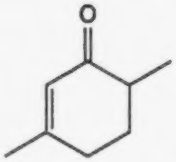
4-Carbethoxy-3,4-dimethyl-2-cyclohexenone (90), 6-carbethoxy-3,6-dimethyl-2-cyclohexenone (91) and 3,6-dimethyl-2-cyclohexenone (92)



90



91



92

A. Intramolecular aldol condensation under acid conditions

To a three-neck round bottom flask equipped with a magnetic stirrer, a Dean-Stark and a condenser, were charged with 3-carbethoxy-3-methyl-2,6-heptadione (1.15 g, 5.4 mmol), *p*-TsOH (0.17 g, 0.9 mmol) and benzene (50 mL). The mixture was heated to reflux under argon for 28 h with azeotropic removal of water and then cooled to room temperature. After being diluted with benzene (20 mL), the mixture was washed with half saturated sodium bicarbonate (20 mL), water (20 mL) and dried over magnesium sulfate. Filtration and concentration gave the crude product mixture which was separated by flash chromatography. Elution with ethyl acetate and hexane (15:85) gave **92** (0.10 g, 15% yield) as a light yellow oil: ir (film) 1672 (C=O, enone) and 1634 cm^{-1} (C=C); ^1H nmr (300 MHz) δ 5.58 (br s, 1 H), 2.20-2.36 (m, 3 H), 2.03 (ddd, J = 13, 9, 4.5 Hz, 1 H), 1.91 (d, J = 1.5 Hz, 3 H), 1.68 (m, 1 H) and 1.10 (d, J = 7 Hz, 3 H); hrms M^+ 124.0892 (calcd. for $C_8H_{12}O$: 124.0887).

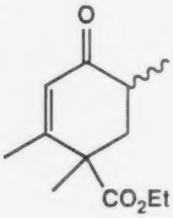
Further elution afforded enone ester **91** (0.60 g, 60% yield) as a yellowish oil: ir ($CHCl_3$ cast) 1730 (C=O, ester) and 1674 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 5.90 (m, 1 H, -C=C**H**CO-), 4.16 (q, J = 7 Hz, 2 H, -OC**H**$_2$CH$_3$), 2.38-2.52 (m, 2 H), 2.25 (ddd, J = 19, 5, 1 Hz, 1 H), 1.96 (br s, 3 H, -CH=CC**H**$_3$), 1.87 (ddd, J = 13, 9, 5 Hz, 1 H), 1.37 (s, 3 H, -C**H**$_3$) and 1.23 (t, J = 7 Hz, 3 H, -OCH$_2$C**H**$_3$); hrms M^+ 196.1099 (calcd. for $C_{11}H_{16}O_3$: 196.1099).

Further elution gave enone ester **90** (0.20 g, 19% yield) as a yellowish oil: ir ($CHCl_3$ cast) 1731 (C=O, ester) and 1677 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 5.91 (q, *J* = 1.5 Hz, 1 H, -C=C**H**CO-), 4.20 (q, *J* = 7 Hz, 2 H, $-OC\mathbf{H}_2CH_3$), 2.35-2.56 (m, 3 H), 1.98 (d, *J* = 1.5 Hz, 3 H, $-CH=CC\mathbf{H}_3$), 1.96 (m, 1 H), 1.45 (s, 3 H, $-C\mathbf{H}_3$) and 1.28 (t, *J* = 7 Hz, 3 H, $-OCH_2C\mathbf{H}_3$); hrms M^+ 196.1100 (calcd. for $C_{11}H_{16}O_3$: 196.1099).

B. Intramolecular aldol condensation using LDA and then dehydration

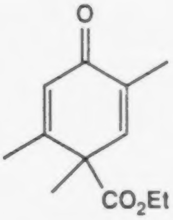
A mixture of diisopropylamine (4.2 mL, 36 mmol) in THF (80 mL) was cooled to 0°C under argon. Then *n*-BuLi (16 mL, 1.9 M in hexane) was added dropwise. The resulting mixture was stirred at 0°C for 15 min and cooled down to -78°C. 3-Carbethoxy-3-methyl-2,6-heptadione (6.42 g, 30 mmol) in THF (70 mL) was then added dropwise to the above LDA solution over a period of 15 min. The mixture was then stirred at -78°C for 3 h and warmed up to 0°C. Saturated ammonium chloride (100 mL) was added and the mixture was extracted with ether (3 x 120 mL). The extracts were combined, washed with water (100 mL) and brine and dried over magnesium sulfate. Filtration and concentration afforded the crude product (6.0 g) which was dehydrated directly as follow. A solution of the crude product (6.0 g) and *p*-TsOH (0.53 g, 2.8 mmol) in benzene (120 mL) was heated to reflux with azeotropic removal of water for 6.5 h. After being cooled to room temperature, the mixture was washed with half saturated sodium bicarbonate (30 mL) and water, and dried over magnesium sulfate. Filtration and evaporation of solvent gave the crude mixture which was separated by flash chromatography. Elution with ethyl acetate and hexane (15:85) gave enone esters **91** (1.0 g, 17% yield) and **90** (3.0 g, 51% yield). A very small amount of enone **92** (< 5% yield) was formed under the reaction conditions.

4-Carbethoxy-3,4,6-trimethyl-2-cyclohexenone (93)



A mixture of diisopropylamine (0.47 mL, 3.33 mmol) in THF (10 mL) was cooled to 0°C under argon. Then *n*-BuLi (1.8 mL, 1.9 M in hexane) was added dropwise. The resulting mixture was stirred for 10 min and then cooled down to -78°C. Enone ester **90** (500 mg, 2.55 mmol) in THF (10 mL) was introduced into the LDA solution over a period of 10 min and the resulting mixture was stirred at -78°C for half an hour. Methyl iodide (0.64 mL) was added in one portion and the mixture was allowed to warm up to 0°C for 2.5 h. Saturated ammonium chlorode (10 mL) was added and the mixture was extracted with ether (2 x 20 mL). The extracts were combined, washed with water, brine and dried over magnesium sulfate. Filtration and concentration gave the crude product which was subjected to flash chromatography. Elution with ethyl acetate and hexane (10:90) afforded a 3:1 mixture of two isomeric enone esters **93** (450 mg, 84% yield) as a colorless oil: ir ($CHCl_3$ cast) 1732 (C=O, ester) and 1678 cm^{-1} (C=O, enone); ^1H nmr (200 MHz) for the major isomer: δ 5.86 (q, *J* = 1.5 Hz, 1 H), 4.15 (q, *J* = 7 Hz, 2 H), 2.32-2.58 (m, 2 H), 2.23 (t, *J* = 13 Hz, 1 H), 1.96 (d, *J* = 1.5 Hz, 3 H), 1.75 (m, 1 H), 1.46 (s, 3 H), 1.24 (t, *J* = 7 Hz, 3 H) and 1.10 (d, *J* = 7 Hz, 3 H); for the minor isomer: δ 5.91 (q, *J* = 1.5 Hz, 1 H), 4.14 (q, *J* = 7 Hz, 2 H), 1.98 (d, *J* = 1.5 Hz, 3 H), 1.39 (s, 3 H), 1.22 (t, *J* = 7 Hz, 3 H) and 1.03 (d, *J* = 7 Hz, 3 H); hrms M^+ 210.1257 (calcd. for $C_{12}H_{18}O_3$: 210.1256). Further elution gave the recovered starting material **90** (50 mg, 10% yield).

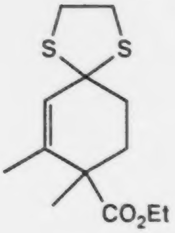
4-Carbethoxy-2,4,5-trimethyl-2,5-hexadienone (89)



A mixture of diisopropylamine (0.64 mL, 4.6 mmol) in THF (20 mL) was cooled to 0°C under argon. Then *n*-BuLi (2.5 mL, 1.8 M in hexane) was added dropwise. The resulting mixture was stirred for 10 min and then cooled down to -78°C. Enone ester **93** (800 mg, 3.8 mmol) in THF (20 mL) was introduced into the LDA solution over a period of 10 min and the resulting mixture was allowed to warm up to 0°C for 20 min and again cooled to -78°C . PhSeCl

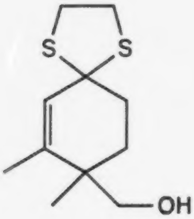
(0.90 g, 4.56 mmol) in THF (10 mL) was added dropwise in 3 min and the mixture was stirred at -78°C for 10 min. Water (45 mL) was added and the mixture was allowed to warm up to room temperature and extracted with ether (3 x 30 mL). The extracts were combined, washed with water, brine and dried over magnesium sulfate. Filtration and concentration gave the crude product (1.6 g) which was subjected to oxidative elimination directly. A solution of the crude product (1.6 g) in THF (25 mL) was cooled to 0°C. Acetic acid (1 mL) was added followed by 30% H_2O_2 (0.6 mL). The mixture was stirred at 0°C for 10 min and then another portion of H_2O_2 (0.6 mL) was added. The mixture was stirred for 1 h and water (5 mL) was added followed by saturated sodium bicarbonate (10 mL). The mixture was extracted with dichloromethane (3 x 15 mL). The extracts were combined, washed with water and dried over magnesium sulfate. Filtration and concentration gave the crude product which was subjected to flash chromatography. Elution with ethyl acetate and hexane (15:85) gave compound **89** (0.3 g, 38% yield) as a light yellow oil: ir (film) 1737 (C=O, ester), 1672 (C=O, enone) and 1640 cm^{-1} (C=C); ^{1}H nmr (200 MHz) δ 6.56 (q, *J* = 1.5 Hz, 1 H, -C**H**=CCO), 6.20 (q, *J* = 1.5 Hz, 1 H, -C=C**H**CO), 4.15 (m, 2 H, -OC**H**$_2$CH$_3$), 1.98 (d, *J* = 1.5 Hz, 3 H), 1.80 (d, *J* = 1.5 Hz, 3 H), 1.48 (s, 3 H) and 1.22 (t, *J* = 7 Hz, 3 H, -OCH$_2$C**H**$_3$); hrms M$^+$ 208.1103 (calcd. for $C_{12}H_{16}O_3$: 208.1099).

4-Carbethoxy-1,1-ethylenedithio-3,4-dimethyl-2-cyclohexene (96)



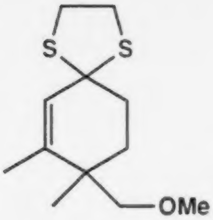
A solution of enone ester **90** (1.0 g, 5.1 mmol) and 1,2-ethanedithiol (0.47 mL, 5.61 mmol) in dichloromethane (20 mL) was cooled to 0°C under an argon atmosphere. $BF_3 \bullet OEt_2$ (0.64 mL, 5.1 mmol) was added and the mixture was stirred at 0°C for 1.5 h. Then 10% ice-cold NaOH (20 mL) was added and organic layer was separated. The aqueous layer was extracted with dichloromethane (2 x 10 mL). The organic layer and the extracts were combined, washed with 10% NaOH (15 mL) and water (20 mL), and dried over magnesium sulfate. Filtration and concentration gave the crude product which was purified by flash chromatography. Elution with ethyl acetate and hexane (5:95) gave thioacetal **96** (1.35 g, 97% yield) as a colorless oil: ir ($CHCl_3$ cast) 1725 cm^{-1} (C=O, ester); ^1H nmr (200 MHz) δ 5.68 (q, *J* = 1.5 Hz, 1 H, -C=C**H**-), 4.13 (q, *J* = 7 Hz, 2 H, $-OC\mathbf{H_2}CH_3$), 3.32 (m, 4 H, $-SC\mathbf{H_2}C\mathbf{H_2}S-$), 2.14-2.36 (m, 3 H), 1.74 (m, 1 H), 1.66 (d, *J* = 1.5 Hz, 3 H, $-CH=CC\mathbf{H_3}$), 1.26 (s, 3 H, $-C\mathbf{H_3}$) and 1.23 (t, *J* = 7 Hz, 3 H, $-OCH_2C\mathbf{H_3}$); hrms M^+ 272.0905 (calcd. for $C_{13}H_{20}O_2S_2$: 272.0905).

1,1-Ethylenedithio-4-(hydroxymethyl)-3,4-dimethyl-2-cyclohexene (97)



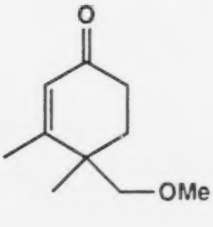
To a suspension of $LiAlH_4$ (0.2 g, 5.0 mmol) in THF (30 mL) under argon at 0°C, was added thioacetal **96** (1.35 g, 5.0 mmol) in THF (20 mL) over a period of 20 min. The mixture was allowed to warm to room temperature and stirred for 2 h. Then water (0.1 mL), 3 N NaOH (0.1 mL), water (0.1 mL) and water (0.1 mL) were added sequentially over a period of 1 h and the resulting grey suspension was stirred for another hour. The mixture was then filtered and the residue washed thoroughly with ether. The filtrate and washing solutions were combined, dried over magnesium sulfate, filtered and concentrated. Flash chromatography using ethyl acetate and hexane (25:75) as an eluent gave alcohol **97** (1.10 g, 95% yield) as a colorless oil: ir ($CHCl_3$ cast) 3423 cm^{-1} (OH); ^1H nmr (300 MHz) δ 5.72 (br s, 1 H, -**CH**=C-), 3.60 (d, *J* = 11 Hz, 1 H, -C**H**HOH), 3.25-3.41 (m, 5 H), 2.16-2.32 (m, 2 H), 2.05 (ddd, *J* = 14, 10, 4 Hz, 1 H), 1.86 (m, 1 H), 1.51 (ddd, *J* = 14, 7, 3 Hz, 1 H), 1.67 (d, *J* = 1.5 Hz, 3 H, -CH=CC**H**$_3$) and 0.98 (s, 3 H, -C**H**$_3$); hrms M^+ 230.0795 (calcd. for $C_{11}H_{18}OS_2$: 230.0799).

1,1-Ethylenedithio-4-(methoxymethyl)-3,4-dimethyl-2-cyclohexene (98)



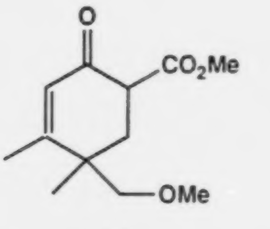
To a suspension of sodium hydride (0.18 g, 60% dispersion in oil, 4.5 mmol) in THF (5 mL) at 0°C under an argon atmosphere, was added alcohol **97** (0.63 g, 2.7 mmol) in THF (5 mL). The mixture was stirred at 0°C for 30 min. Then methyl iodide (0.77 g, 5.4 mmol) was added in one portion and the resulting mixture was stirred for an additional 30 min. Then saturated ammonium chloride (10 mL) was added and the mixture was extracted with dichloromethane (3 x 15 mL). The extracts were combined, washed with water, dried over magnesium sulfate and concentrated to give the crude product which was purified by flash chromatography. Elution with ethyl acetate and hexane (10:90) gave compound **98** (0.61 g, 91% yield) as a colorless oil: ^{1}H nmr (200 MHz) δ 5.62 (br s, 1 H), 3.20-3.40 (m, 8 H), 3.10 (d, J = 8 Hz, 1 H), 1.98-2.28 (m, 3 H), 1.76 (d, J = 1.5 Hz, 3 H), 1.50 (m, 1 H) and 1.00 (s, 3 H).

4-(Methoxymethyl)-3,4-dimethyl-2-cyclohexenone (99)

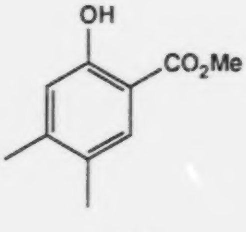


A mixture of compound **98** (0.51 g, 2.09 mmol) and Ag_2O (4.84 g, 20.9 mmol) in methanol and water (10:1, 25 mL) was stirred at room temperature under argon for 1 day and filtered. The filtrate was extracted with dichloromethane (3 x 15 mL). The extracts were combined and dried over magnesium sulfate. Filtration and concentration gave the crude product which was subjected to chromatography. Elution with ethyl acetate and hexane (10:90) gave recovered starting material (0.12 g, 24% yield). Further elution afforded enone **99** (0.12 g, 35% yield) as a colorless oil: ir ($CHCl_3$ cast) 1670 (C=O, enone) and 1620 cm^{-1} (C=C); ^1H nmr (200 MHz) δ 5.87 (br s, 1 H, -C=C**H**CO-), 3.46 (d, *J* = 9 Hz, 1 H, -C**H**HOMe), 3.34 (s, 3 H, -OC**H**$_3$), 3.16 (d, *J* = 9 Hz, 1 H, -CH**H**OMe), 2.42-2.50 (m, 2 H), 2.28 (m, 1 H), 1.93 (d, *J* = 1.3 Hz, 3 H, -CH=CC**H**$_3$), 1.70 (m, 1 H) and 1.12 (s, 3 H, -C**H**$_3$); hrms M^+ 168.1149 (calcd. for $C_{10}H_{16}O_2$: 168.1150).

6-Carbomethoxy-4-(methoxymethyl)-3,4-dimethyl-2-cyclohexenone (100) and methyl 2-hydroxy-3,4-dimethyl-benzoate (101)



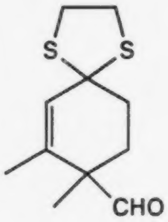
100



101

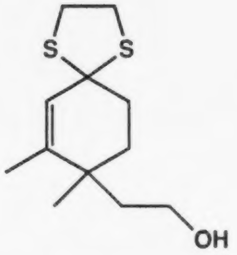
To a suspension of sodium hydride (0.36 g, 60% dispersion in oil, 8.93 mmol) in DME (9 mL) under an argon atmosphere, was added dimethyl carbonate (0.45 mL, 5.37 mmol). The mixture was brought to a boil and then enone **99** (0.30 g, 1.79 mmol) in DME (6 mL) was added dropwise over a period of 5 min. The mixture was refluxed for 20 h and cooled to 0°C. 1 N HCl was added to the mixture slowly until the solution turned acidic. The mixture was extracted with dichloromethane (3 x 10 mL). The extracts were combined, washed with water and brine, and dried over magnesium sulfate. Filtration and concentration afforded the crude product which was purified by flash chromatography. Elution with ethyl acetate and hexane (15:85) gave keto ester **100** (0.15 g, 40% yield, a mixture of three isomers) as a yellowish oil: ^{1}H nmr (80 MHz) δ 11.75 (s), 5.95 (m), 5.85 (m), 5.75 (m), 3.75 (s, 3 H, $-CO_2C\mathbf{H}_3$), 3.30 (s, 3 H, $-OC\mathbf{H}_3$), 3.50-3.10 (m, 2 H), 1.70-2.74 (m), 1.90 (br s, 3 H), 1.20 (s, 3 H, $-C\mathbf{H}_3$). To a solution of PhSeCl (118 mg, 0.604 mmol) in dichloromethane (5 mL) at 0°C under an argon atmosphere, was added pyridine (50 mg, 0.63 mmol). The mixture was stirred at 0°C for 15 min. Keto ester **100** (0.13 g, 0.58 mmol) in dichloromethane (3 mL) was introduced to the above solution and the mixture was stirred for 45 min. The mixture was washed with 1 N HCl (2 x 5 mL) and cooled to 0°C. 30% H_2O_2 (0.1 mL) was added in a 10 min interval for four times. Then water (5 mL) was added to the solution and the organic layer was separated and washed with saturated sodium bicarbonate (5 mL). Evaporation of solvent gave the crude product which was purified by flash chromatography. Elution with ethyl acetate and hexane (30:70) gave compound **101** (66 mg, 64% yield) as a light yellow oil: ir ($CHCl_3$ cast) 3200 (OH), 1674 (C=O, ester), 1620 and 1580 cm^{-1} (aromatic C-H bending); ^1H nmr (80 MHz) δ 10.46 (s, 1 H, **OH**), 7.60 (s, 1 H), 6.80 (s, 1 H), 3.95 (s, 3 H, -OC**H**$_3$), 2.28 (s, 3 H, -C**H**$_3$) and 2.20 (s, 3 H, -C**H**$_3$); hrms M^+ 180.0784 (calcd. for $C_{10}H_{12}O_3$: 180.0786).

1,1-Ethylenedithio-4-formyl-3,4-dimethyl-2-cyclohexene (102)



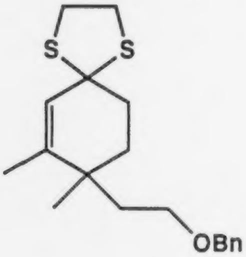
To a solution of alcohol **97** (1.0 g, 4.35 mmol) in dichloromethane (40 mL), was added PCC on alumina (7.26 g, 0.97 mmol/g, 7.05 mmol). The mixture was stirred at room temperature under argon for 10 h and filtered through Florisil. The Florisil was eluted with additional dichloromethane (50 mL). The filtrate and washing solution were combined and concentrated to give aldehyde **102** (0.72 g, 72% yield) as a yellowish oil: ir ($CHCl_3$ cast) 1724 cm^{-1} (C=O, aldehyde); ^1H nmr (300 MHz) δ 9.42 (s, 1 H, -C**HO**), 5.86 (q, *J* = 1.5 Hz, 1 H, -C=C**H**-), 3.28-3.43 (m, 4 H, -SC**H**$_2$C**H**$_2$S-), 2.04-2.33 (m, 3 H), 1.65 (d, *J* = 1.5 Hz, 3 H, -CH=CC**H**$_3$), 1.64 (m, 1 H) and 1.19 (s, 3 H, -C**H**$_3$); hrms M^+ 228.0640 (calcd. for $C_{11}H_{16}OS_2$: 228.0642). Further elution of the Florisil gave the recovered starting alcohol (0.1 g, 10%).

1,1-Ethylenedithio-4-(2-hydroxyethyl)-3,4-dimethyl-2-cyclohexene (104)



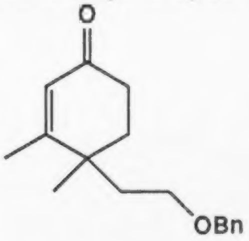
To a solution of methoxymethyltriphenylphosphonium chloride (2.45 g, 6.8 mmol) in THF (18 mL) was added *n*-BuLi (2.8 mL, 1.9 M in hexane, 5.32 mmol) at 0°C under an argon atmosphere. The mixture was stirred for 30 min and then aldehyde **102** (0.62 g, 2.72 mmol) in THF (15 mL) was introduced to the solution over a period of 15 min. The mixture was then stirred for an additional 2 h. Saturated ammonium chloride (20 mL) was added and the mixture was partitioned between ethyl acetate and water. The organic layer was dried over magnesium sulfate, filtered and concentrated. Initial attempts to separate the enol ether by flash chromatography using ethyl acetate and hexane (5:95) as an eluent gave enol ether **103** (0.71 g) as a mixture of *cis* and *trans* isomers which was contaminated by triphenylphosphine oxide. Therefore, the mixture was hydrolyzed directly using concentrated HCl. The enol ether was dissolved in ether (5 mL) and then 2 N HCl (2 mL) was added followed by concentrated HCl (3 mL). The mixture was stirred at room temperature for 26 h and extracted with ether (2 x 10 mL). The extracts were combined, washed with water and saturated sodium bicarbonate, and dried over magnesium sulfate. Filtration and concentration gave the crude product (0.53 g) which was reducd by sodium borohydride directly. To a solution of the crude product (0.53 g) in ethanol (5 mL) at 0°C, was added sodium borohydride (0.13 g, 3.29 mmol). The mixture was stirred for 5 min and then saturated ammonium chloride (5 mL) was added cautiously to the reaction mixture. Ethanol was removed *in vacco* and the residue was extracted by dichlomethane (2 x 10 mL). The extracts were combined and concentrated to give the crude product which was purified by chromatography. Elution with ethyl acetate and hexane (50:50) gave alcohol **104** (0.38 g, 57% yield from aldehyde **102**) as a colorless oil: ir ($CHCl_3$ cast) 3260-3415 cm^{-1} (br, OH); ^1H nmr (200 MHz) δ 5.59 (br s, 1 H, -C**H**=C-), 3.52-3.78 (m, 2 H, -C$\mathbf{H}_2$OH), 3.20-3.42 (m, 4 H, -SC$\mathbf{H}_2$C$\mathbf{H}_2$S-), 2.17 (m, 2 H), 1.69 (d, J = 1.5 Hz, 3 H, -CH=CC$\mathbf{H}_3$), 1.46-2.00 (m, 5 H) and 1.08 (s, 3 H, -C$\mathbf{H}_3$); hrms M^+ 244.0959 (calcd. for $C_{12}H_{20}OS_2$: 244.0956).

4-(2-Benzyloxyethyl)-1,1-ethylenedithio-3,4-dimethyl-2-cyclohexene (105)



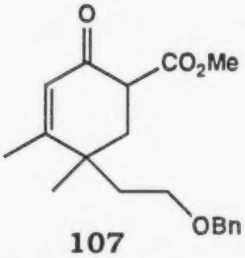
To a suspension of sodium hydride (89 mg, 60% dispersion in oil, 2.21 mmol) in THF (5 mL) was added alcohol **104** (0.36 g, 1.48 mmol) in THF (10 mL) at 0°C under an argon atmosphere. The mixture was stirred for 30 min and then benzyl bromide (0.36 mL, 2.96 mmol) was added in one portion followed by tetrabutylammonium iodide (55 mg, 0.15 mmol). The mixture was stirred at room temperature overnight and water was then added. The mixture was extracted with dichloromethane (3 x 10 mL). The extracts were combined, washed with water, dried over magnesium sulfate and filtered. Concentration of the filtrate gave the crude product which was subjected to chromatography. Elution with ethyl acetate and hexane (5:95) gave compound **105** (0.43 g, 87% yield) as a yellowish oil: ir ($CHCl_3$ cast) 1638 (C=C), 1111, 1099, 1076, 736, 696 cm^{-1}; ^1H nmr (200 MHz) δ 7.35 (m, 5 H, C_6H_5-), 5.57 (br s, 1 H, -C**H**=C-), 4.50 (s, 2 H, $-OCH_2C_6H_5$), 3.20-3.60 (m, 2 H), 2.17 (m, 2 H), 1.65 (d, J = 1 Hz, 3 H, $-CH{=}CCH_3$), 1.46-2.00 (m, 4 H) and 1.05 (s, 3 H, $-CH_3$); hrms M^+ 334.1433 (calcd. for $C_{19}H_{26}OS_2$: 334.1425).

4-(2-Benzyloxyethyl)-3,4-dimethyl-2-cyclohexenone (106)

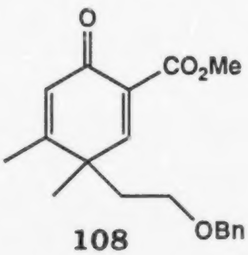


To a solution of compound **105** (0.38 g, 1.14 mmol) in CH_3CN-H_2O (4:1, 4 mL) was added calcium carbonate (0.284 g, 2.84 mmol) followed by $HgCl_2$ (0.772 g, 2.84 mmol) in CH_3CN-H_2O (2 mL). The mixture was stirred at room temperature for 2 h and filtered. The filtrate was partitioned between water and dichloromethane. The dichloromethane layer was washed with water and concentrated to afford the crude product which was purified by chromatography. Elution with ethyl acetate and hexane (30:70) gave enone **106** (0.21 g, 70% yield) as a colorless oil: ir ($CHCl_3$ cast) 1665 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 7.31 (m, 5 H, C_6H_5-), 5.30 (q, J = 1 Hz, 1 H, -C=C**H**CO), 4.48 (s, 2 H, -OC$\mathbf{H}_2C_6H_5$), 3.44-3.60 (m, 2 H, -$OCH_2C\mathbf{H}_2OBn$), 2.43 (t, J = 7 Hz, 2 H), 1.80 (d, J = 1 Hz, 3 H, -CH=CC$\mathbf{H}_3$), 1.70-2.08 (m, 4 H) and 1.19 (s, 3 H, -C$\mathbf{H}_3$); hrms M^+ 258.1623 (calcd. for $C_{17}H_{22}O_2$: 258.1620).

4-(2-Benzyloxyethyl)-6-carbomethoxy-3,4-dimethyl-2-cyclohexenone (107) and 4-(2-benzyloxyethyl)-2-carbomethoxy-4,5-dimethyl-2,5-cyclohexadienone (108)



107



108

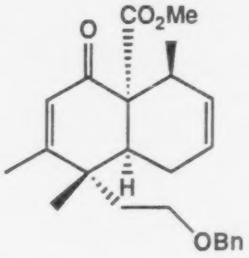
To a suspension of sodium hydride (55 mg, 60% oil dispersion, 1.37 mmol) in DME (2 mL), was added dimethyl carbonate (0.18

mL, 2.06 mmol) under an argon atmosphere. The mixture was brought to a boil and then enone **106** (0.18 g, 0.69 mmol) in DME (3 mL) was added dropwise. The resulting mixture was refluxed for 23 h and cooled down to 0°C. 1 N HCl was added until the mixture was acidic (pH~4). The mixture was extracted with dichloromethane (3 x 10 mL). The extracts were combined, washed with water and concentrated. Flash chromatography using ethyl acetate and hexane (20:80) as an eluent gave keto ester **107** (0.19 g, 86% yield) as a light yellow oil: ir ($CHCl_3$ cast) 1743 (C=O, ester), 1672 (C=O, enone) 1618-1600 cm^{-1} (C=C of β-keto ester); ^1H nmr (300 MHz) (a mixture of three isomers) δ 11.73 (s), 7.30 (m, 5 H), 5.83 (m), 5.74 (m), 4.45-4.48 (3s), 3.77 (s), 3.73 (s), 3.71 (s), 3.4[illegible]-3.66 (m), 2.45 (dd, *J* = 16, 14 Hz), 2.20 (m), 1.70-2.00 (m,) 1.24 (s), 1.18 (s) and 1.08 (s); hrms M^+ 316.1677 (calcd. for $C_{19}H_{24}O_4$: 316.1674).

The following procedure will be referred to as the standard procedure for the introduction of a double bond *via* phenylselenenylation and oxidative-elimination by H_2O_2. To a solution of PhSeCl (113 mg, 0.56 mmol) in dichloromethane (5 mL) at 0°C under an argon atmosphere, was added pyridine (41.8 mL, 0.52 mmol). The mixture was stirred at 0°C for 15 min and then keto ester **107** (0.15 g, 0.47 mmol) in dichloromethane (5 mL) was added. The mixture was stirred for 1 h and then 1N HCl (5 mL) was added. The organic layer was separated, washed with 1 N HCl (5 mL) and cooled to 0°C again. 30% H_2O_2 (0.1 mL) was added in a

10 min interval for 4 times. Then water (5 mL) was added to the reaction mixture and the solution was extracted with dichloromethane (2 x 10 mL). The extracts were combined, washed with water, saturated sodium bicarbonate and concentrated. The crude product was purified by chromatography. Elution with ethyl acetate and hexane (40:60) gave recovered starting material **107** (25 mg, 23% yield). Further elution gave dienone ester **108** (100 mg, 67% yield) as a light yellow oil: ir ($CHCl_3$ cast) 1741 (C=O, ester), 1668 (C=O, enone) and 1636 cm^{-1} (C=C); ^1H nmr (200 MHz) δ 7.54 (s, 1 H, -**C****H**=CCO), 7.28 (m, 5 H, C_6H_5-), 6.21 (q, *J* = 1.5 Hz, 1 H, -C=C**H**CO), 4.34 (s, 2 H, -OC**H**$_2$$C_6H_5$), 3.82 (s, 3 H, -OC**H**$_3$), 3.21 (m, 2 H, -C**H**$_2$OBn), 2.21 (m, 1 H), 2.02 (m, 1 H), 2.00 (d, *J* = 1.5 Hz, 3 H, -CH=CC**H**$_3$) and 1.34 (s, 3 H, -C**H**$_3$); hrms M^+ 314.1513 (calcd. for $C_{19}H_{22}O_4$: 314.1518).

(1R*,5S*,6S*,10S*)-5-(2-Benzyloxyethyl)-1-carbomethoxy-4,5,10-trimethylbicyclo[4.4.0]deca-3,8-dien-2-one (109)



A. Using $ZnCl_2$ as catalyst

$ZnCl_2$ (80 mg, 0.60 mmol) in a three-neck round bottom flask was fused under argon and then cooled to room temperature. Dry dichloromethane (3 mL) was added and the $ZnCl_2$ was crushed using a spatula to small pieces. The suspension was stirred for 10 min until a cloudy fine suspension formed. Then the mixture was cooled to 0°C and dienone ester **108** (95 mg, 0.30 mmol) in dichloromethane (2 mL) was added dropwise. The cloudy suspension turned clear presumably due to the complexation of the dienophile and $ZnCl_2$. *trans*-Piperylene (0.3 mL, 3 mmol) was added and the resulting mixture was stirred under argon at room temperature for 25 h. Water (5 mL) was added and the mixture was extracted with dichloromethane (2 x 5 mL). The extracts were combined, washed with brine and concentrated. Flash chromatography using ethyl acetate and hexane (20:80) gave adduct **109** (84.3 mg, 73% yield) as a light yellow oil: ir ($CHCl_3$ cast) 1726 (C=O, ester), 1681 (C=O, enone) and 1620 cm^{-1} (C=C); ^1H nmr (300 MHz) δ 7.35 (m, 5 H, C_6H_5-), 5.83 (q, J = 1.5 Hz, 1 H, -C=**C**HCO), 5.57 (ddd, J = 10, 4.5, 2 Hz, 1 H), 5.49 (ddd, J = 10, 7, 3 Hz, 1 H), 4.54 (d, J = 13 Hz, 1 H, benzylic), 4.49 (d, J = 13 Hz, 1 H, benzylic), 3.69 (s, 3 H, -OC**H**$_3$), 3.58-3.74 (m, 2 H, -OCH_2C**H**$_2$OBn), 2.74 (m, 2 H), 2.19 (m, 1 H), 1.97 (m, 1 H), 1.85 (m, 1 H), 1.84 (d, J = 1.5 Hz, -CH=CC**H**$_3$), 1.69 (ddd, J = 14, 9, 6 Hz, 1 H), 1.25 (d, J = 7 Hz, 3 H, -CHC**H**$_3$) and 1.12 (s, 3 H, -C**H**$_3$); ^{13}C nmr (APT) δ 195.59 (p), 174.59 (p), 160.87 (p), 138.38 (p), 130.69 (a), 128.43 (a), 127.65 (a), 127.17 (a), 123.74 (a), 73.30 (p), 66.72 (p), 59.12 (p), 52.38 (a), 43.51 (a), 42.52 (p), 38.43 (a), 37.40 (p), 27.18 (p), 23.50 (a), 19.33 (a) and 17.07 (a); hrms M^+

382.2147 (calcd. for $C_{24}H_{30}O_4$: 382.2144). Further elution gave the recovered dienone ester **108** (13 mg, 16% yield).

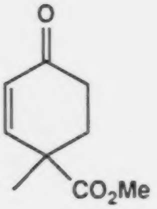
B. Using $FeCl_3$ as catalyst

To a solution of ferric chloride (48 mg, 0.30 mmol) in dichloromethane (5 mL) at 0°C under an argon atmosphere, were added dienone ester **108** (77.9 mg, 0.245 mmol) in dichloromethane (5 mL) and *trans*-piperylene (0.25 mL, 2.45 mmol). The solution turned into dark green instantly. The mixture was stirred at 0°C for 2 h and then 2 N HCl (5 mL) was added. The mixture was extracted with dichloromethane (3 x 10 mL). The extracts were combined, washed with water, saturated sodium bicarbonate and dried over magnesium sulfate. Filtration and concentration gave the crude product which was purified by chromatography to give adduct **109** (55.3 mg, 58% yield) as a yellowish oil.

C. Using $AlCl_3$ as catalyst

To a solution of $AlCl_3$ (38 mg, 0.28 mmol) in dichloromethane (5 mL) at 0°C under an argon atmosphere, were added dienone ester **108** (85 mg, 0.28 mmol) in dichlomethane (3 mL) and *trans*-piperylene (0.3 mL, 3 mmol). The mixture was stirred at 0°C for 8 h and 2 N HCl (5 mL) was added. Work-up as described followed by chromatography gave adduct **109** (47 mg, 45% yield) as a light yellow oil.

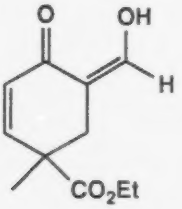
4-Carbomethoxy-4-methyl-2-cyclohexenone (112)



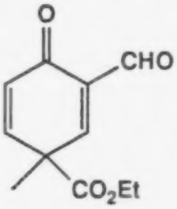
A round bottom Pyrex high pressure tube filled with *trans*-1-methoxy-3-(trimethylsilyoxy)-1,3-butadiene (2.1 g, 90% pure, 12 mmol), methyl methacrylate (4.8 g, 48 mmol), a few crystals of dinitrobenzene (DNB) and benzene (2 mL) was cooled down to -196°C (liquid nitrogen), degassed under high vacuum (5 micron) and sealed. The tube was allowed to warm up to room temperature and then put into a 90°C oil bath for 44 h. After being cooled down to room temperature, the volatiles were removed by bulb-to-bulb distillation. The residue was dissolved in THF-0.005 N HCl (4:1, 30 mL) and the mixture was stirred at room temperature for 1 h. Most of the THF was removed *in vacuo* and the remaining mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 20 mL). The extracts were combined and washed with water. Concentration gave the crude product which was purified by flash chromatography. Elution with ethyl acetate and hexane (20:80) gave product **112** (1.85 g, 92% yield from diene) as a colorless oil: ir ($CHCl_3$ cast) 1733 (C=O, ester), 1685 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 6.89 (d, J = 10 Hz, 1 H), 5.99 (d, J = 10 Hz, 1 H), 3.75 (s, 3 H), 2.42-2.58 (m, 2 H), 1.92-

2.06 (m, 2 H) and 1.45 (s, 3 H); hrms M^+ 168.0786 (calcd. for $C_9H_{12}O_3$: 168.0786). Anal. calcd. for $C_9H_{12}O_3$: C 64.27, H 7.19; found: C 64.03, H 7.17.

4-Carbethoxy-6-formyl-4-methyl-2-cyclohexenone (113) and 4-carbethoxy-2-formyl-4-methyl-2,5-cyclohexadienone (114)



113

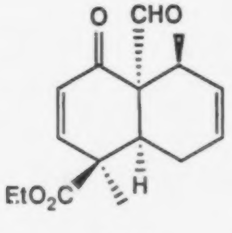


114

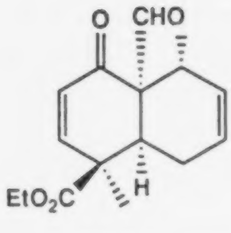
A suspension of sodium hydride (0.16 g, 60% dispersion inn oil, 4.0 mmol) in ethyl formate (10.6 mL, 132 mmol) was stirred at 0°C for 1 h under an argon atmosphere. Enone ester **112** (0.34 g, 2.0 mmol) in THF or DME (7 mL) and a few drops of ethanol were introduced. The mixture was stirred at 0°C for 30 min and then at room temperature for 23 h. Saturated ammonium chloride (10 mL) was added and the mixture was extracted with ether (3 x 20 mL). The extracts were combined, washed with brine, dried over magnesium sulfate and concentrated. Flash chromatography of the crude product using ethyl acetate and hexane (10:90) as an eluent gave keto aldehyde **113** (0.46 g, 100% yield) as a yellowish oil: ir ($CHCl_3$ cast) 1732 (C=O, ester), 1650 (C=O, enone), 1623-1574 cm^{-1} (C=C, enol); ^1H nmr (80 MHz) δ 13.60 (br s, 1 H), 7.62 (br s, 1 H), 6.82 (d, J = 10 Hz, 1 H), 6.11 (d, J = 10 Hz, 1 H), 4.20 (q, J =

7 Hz, 2 H), 2.90 (d, J = 14.5 Hz, 1 H), 2.49 (d, J = 14.5 Hz, 1 H), 1.38 (s, 3 H) and 1.30 (t, J = 7 Hz, 3 H); hrms M^+ 210.0892 (calcd. for $C_{11}H_{14}O_4$: 210.0892). Phenylselenenylation-oxidative elimination of **113** using the standard procedure discribed previously gave dienone aldehyde **114** (0.34 g, 81% yield overall from enone ester **112**) as a colorless oil: ir ($CHCl_3$ cast) 1736 (C=O, ester), 1708 (C=O, aldehyde), 1669 cm^{-1} (C=O, enone); ^1H nmr (80 MHz) δ 10.25 (s, 1 H, -C**H**O), 7.80 (d, J = 3 Hz, 1 H, -C**H**=C(CO)CHO), 7.25 (dd, J = 10, 3 Hz, 1 H, -C**H**=CHCO), 6.35 (d, J = 10 Hz, 1 H, -CH=C**H**CO), 4.25 (q, J = 7 Hz, 2 H), 1.65 (s, 3 H, -C**H**$_3$), 1.30 (t, J = 7 Hz, 3 H); hrms m/z 135.0448 (M^+-CO_2Et, calcd. for $C_8H_7O_2$: 135.0446); cims $[M+NH_4]^+$ 226.

(1S*,5S*,6S*,10S*)-5-Carbethoxy-1-formyl-5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (115) and (1S*,5S*,6S*,10R*)-5-carbethoxy-1-formyl-5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (116)



115



116

A. Thermal reaction

A solution of dienone aldehyde **114** (113 mg, 0.54 mmol) and *trans*-piperylene (0.54 mL, 5.43 mmol) in benzene (4 mL) was heated to reflux for 24 h under an argon atmosphere and then cooled to room temperature. The volatiles were removed *in vacuo* and the residue was purified by chromatography. Elution with ethyl acetate and hexane (15:85) gave adducts **115** and **116** (0.138 g, 93% yield) as a colorless oil: ir ($CHCl_3$ cast) 1727 (C=O, ester and aldehyde), 1690 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) (a mixture of two isomers in a ratio of 4.7:1); for the major isomer **115**: δ 9.66 (s, 1 H, -C**H**O), 6.86 (dd, *J* = 10, 2 Hz, 1 H, -C**H**=CHCO), 5.98 (d, *J* = 10 Hz, 1 H, -CH=C**H**CO), 5.59 (ddd, *J* = 10, 3, 2 Hz, 1 H), 5.50 (ddd, *J* = 10, 6, 3 Hz, 1 H), 4.12-4.15 (m, 2 H), 3.00 (ddd, *J* = 10, 6, 2 Hz), 2.71 (m, 1 H), 2.20 (m, 1 H), 2.05 (m, 1 H), 1.46 (s, 3 H, -C**H**$_3$), 1.31 (t, *J* = 7 Hz, 3 H) and 1.28 (d, *J* = 7 Hz, 3 H, -CHC**H**$_3$); for the minor isomer **116**: δ 9.85 (s, 1 H, -C**H**O), 6.84 (dd, *J* = 10, 1 Hz, 1 H, -C**H**=CHCO), 6.02 (d, *J* = 10 Hz, 1 H, -CH=C**H**CO), 5.50-5.60 (m, 2 H), 4.05-4.15 (m, 2 H), 3.06 (m, 1 H), 2.97 (dd, *J* = 6, 6 Hz), 1.98-2.34 (m, 2 H), 1.45 (s, 3 H), 1.33 (t, *J* = 7 Hz, 3 H) and 1.17 (d, *J* = 7 Hz, 3 H); hrms M^+ 276.1364 (calcd. for $C_{16}H_{20}O_4$: 276.1361).

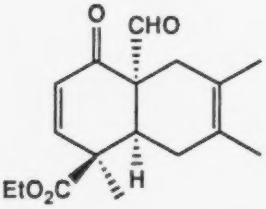
B. Using $ZnCl_2$ as catalyst

$ZnCl_2$ (120 mg, 0.87 mmol) in a three-neck round bottom flask was fused under argon and then cooled to room temperature. Dry dichloromethane (5 mL) was added and the $ZnCl_2$ was crushed using a spatula to small pieces. The suspension was stirred for 10 min until a cloudy fine suspension formed. Then the mixture was cooled to 0°C and dienone aldehyde **114** (60 mg, 0.29 mmol) in dichloromethane (2 mL) was added dropwise. The cloudy suspension turned clear presumably due to the complexation of the dienophile and $ZnCl_2$. *trans*-Piperylene (0.3 mL, 3 mmol) was added and the resulting mixture was stirred under argon at 0°C for 5 h. Water (5 mL) was added to the above solution and the mixture was extracted with dichloromethane (3 x 5 mL). The extracts were combined, washed with water and dried over magnesium sulfate. Filtration and concentration afforded the crude product which was subjected to chromatography. Elution with ethyl acetate and hexane (15:85) gave adduct **115** (75 mg, 95% yield) as a colorless oil: ^{13}C nmr (APT) δ 201.35 (a), 196.28 (p), 173.27 (p), 147.23 (a), 130.36 (a), 128.07 (a), 123.71 (a), 64.35 (p), 61.54 (p), 48.80 (p), 43.47 (a), 33.79 (a), 25.99 (p), 25.66 (a), 16.71 (a) and 14.10 (a).

C. Using $FeCl_3$ as catalyst

A solution of $FeCl_3$ (75 mg, 0.46 mmol) in dichloromethane (2 mL) was cooled to -78°C under argon. *trans*-Piperylene (0.25 mL, 2.31 mmol) was added followed immediately by the addition of dienone aldehyde **114** (48 mg, 0.23 mmol) in dichloromethane (2 mL). The mixture was stirred at -78°C for 2 h and 1 N HCl (5 mL) was added. After being warmed up to 0°C, the mixture was extracted with dichloromethane (3 x 5 mL). The extracts were combined, washed with water and dried over magnesium sulfate. Filtration and concentration gave the crude product which was purified by chromatography to afford adduct **115** (35 mg, 55% yield) as a light yellow oil.

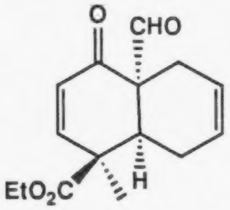
(1S*,5S*,6S*)-5-Carbethoxy-1-formyl-5,8,9-trimethylbicyclo[4.4.0]deca-3,8-dien-2-one (117)



A solution fo dienone aldehyde (42 mg, 0.20 mmol) and 2,3-dimethyl-1,3-butadiene (166 mg, 2.0 mmol) in benzene was heated under reflux for 45 h under an argon atmosphere and cooled to room temperature. The volatiles were removed *in vacuo* and the residue was subjected to chromatography. Elution with ethyl acetate and hexane (15:85) gave adduct **117** (35 mg, 60% yield) as a light yellowish oil: ir ($CHCl_3$ cast) 1730 (C=O, ester and aldehyde), 1685 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 9.60 (s, 1 H, -C**H**O), 6.83 (d, *J* = 10 Hz, 1 H, -C**H**=CHCO), 6.02 (d, *J* = 10 Hz, 1 H, -CH=C**H**CO), 4.09 (q, *J* = 7 Hz, 2 H), 2.85 (dd, *J* = 6, 5 Hz, 1 H), 2.55 (br d, *J* = 17 Hz, 1 H), 2.28 (br d, *J* = 17 Hz, 1 H), 2.16 (br d, *J* = 18 Hz), 2.01 (br d, *J* = 18 Hz, 1 H), 1.63 (br s, 3 H), 1.53 (br s, 3 H), 1.47 (s, 3 H, -C**H**$_3$) and 1.27 (t, *J* = 7 Hz, 3 H); ^{13}C nmr (APT) δ 200.68 (a), 197.09 (p), 172.84 (p), 150.79 (a), 126.54 (a), 124.53 (p), 122.06 (p), 61.65 (p), 60.13 (p), 46.63 (p), 40.67 (a), 32.07 (p), 29.89 (p), 26.34 (a), 18.88 (a), 18.61 (a) and 13.97 (a); hrms

M+ 290.1512 (calcd. for $C_{17}H_{22}O_4$: 290.1518). Further elution gave the recovered **114** (13 mg, 30% yield).

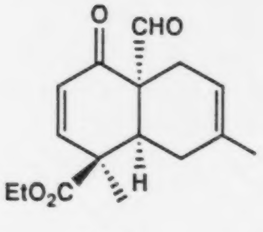
(1S*,5S*,6S*)-5-Carbethoxy-1-formyl-5-methylbicyclo[4.4.0]deca-3,8-dien-2-one (118)



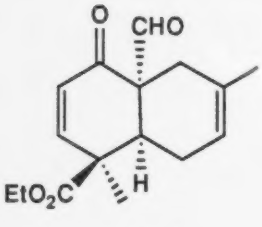
To a three-neck round bottom flask equipped with a magnetic stirrer and a dry-ice condenser, was charged with $ZnCl_2$ (150 mg, 0.79 mmol). The $ZnCl_2$ was fused under an argon atmosphere and cooled to room temperature. Dichloromethane (5 mL) was added and the $ZnCl_2$ was crushed into small pieces by a spatula. The suspension was stirred at room temperature for 15 min and cooled to 0°C. Dienone aldehyde **114** (55 mg, 0.26 mmol) in dichloromethane (2 mL) was added to the above suspension followed by bubbling 1,3-butadiene into the solution until condensation on the dry-ice condenser started. The mixture was warmed up slowly to room temperature and stirred for 18 h. Water (5 mL) was added and the mixture was extracted with dichloromethane (3 x 5 mL). The extracts were combined, washed with water and brine, and dried over magnesium sulfate. Filtration and concentration gave the crude product which was subjected to chromatography. Elution with ethyl acetate and hexane (15:85) gave adduct **118** (59 mg, 85% yield) as a colorless oil: ir ($CHCl_3$

cast) 1728 (C=O, ester and aldehyde) and 1687 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz) δ 9.61 (s, 1 H, -C**H**O), 6.83 (d, *J* = 10 Hz, 1 H, -C**H**=CHCO), 6.04 (d, *J* = 10 Hz, 1 H, -CH=C**H**CO), 5.66 (m, 1 H), 5.56 (m, 1 H), 4.13 (q, *J* = 7 Hz, 2 H), 2.89 (dd, *J* = 7, 5 Hz, 1 H), 2.65 (dm, *J* = 18 Hz, 1 H), 2.38 (dm, *J* = 18 Hz, 1 H), 2.31 (dm, *J* = 19 Hz, 1 H), 2.13 (dm, *J* = 19 Hz, 1 H), 1.49 (s, 3 H, -C**H**$_3$) and 1.28 (t, *J* = 7 Hz, 3 H); ^{13}C nmr (APT) δ 200.33 (a), 196.86 (p), 172.77 (p), 150.79 (a), 126.46 (a), 125.71 (a), 122.60 (a), 61.76 (p), 59.33 (p), 46.76 (p), 39.75 (a), 26.22 (a), 25.95 (p), 23.45 (p) and 13.90 (a); hrms M$^+$ 262.1200 (calcd. for $C_{15}H_{18}O_4$: 262.1205). Anal. calcd. for $C_{15}H_{18}O_4$: C 68.69, H 6.92; found: C 68.49, H 6.91. Further elution gave the recovered enone aldehyde **114** (3 mg, 5% yield).

(1S*,5S*,6S*)-5-Carbethoxy-1-formyl-5,8-dimethylbicyclo[4.4.0]-deca-3,8-dien-2-one (119) and (1S*,5S*,6S*)-5-carbethoxy-1-formyl-5,9-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (120)



119



120

A. Thermal reaction

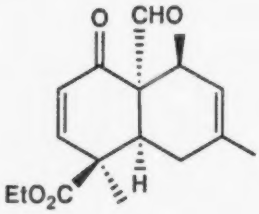
A solution of dienone aldehyde **114** (43 mg, 0.21 mmol) and isoprene (0.42 mL, 4.13 mmol) in benzene (3 mL) was heated under reflux under an argon atmosphere for 42 h and cooled to room temperature. The volatiles were evaporated in *vacuo* and the residue was subjected to chromatography. Elution with ethyl acetate and hexane (20:80) gave adducts **119** and **120** (16 mg, 28% yield) as a light yellow oil: ir ($CHCl_3$ cast) 1728 (C=O, ester and aldehyde), 1687 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) (two isomers in a ratio of 2.2:1); for the major adduct **119**: δ 9.60 (s, 1 H), 6.80 (d, J = 10 Hz, 1 H), 6.02 (d, J = 10 Hz, 1 H), 5.35 (m, 1 H), 4.05-4.20 (m, 2 H), 2.88 (dd, J = 6.5, 5 Hz, 1 H), 2.61 (dm, J = 18 Hz, 1 H), 2.40 (dm, J = 18 Hz, 1 H), 2.18 (dm, J = 18 Hz, 1 H), 2.02 (dm, J = 18 Hz, 1 H), 1.57 (br s, 3 H) and 1.49 (s, 3 H); for the minor adduct **120**: δ 9.59 (s, 1 H), 6.83 (d, J = 10 Hz, 1 H), 6.05 (d, J = 10 Hz, 1 H), 5.24 (m, 1 H), 4.05-4.20 (m, 2 H), 2.81 (dd, J = 6.5, 5.5 Hz, 1 H), 2.61 (dm, J = 18 Hz, 1 H), 2.54 (dm, J = 18 Hz, 1 H), 2.26 (dm, J = 18 Hz, 1 H), 2.09 (dm, J = 18 Hz, 1 H), 1.67 (br s, 3 H) and 1.48 (s, 3 H); hrms M^+ 276.1365 (calcd. for $C_{16}H_{20}O_4$: 276.1361). Further elution gave recovered enone aldehyde **114** (28 mg, 67% yield).

B. Using $ZnCl_2$ as catalyst

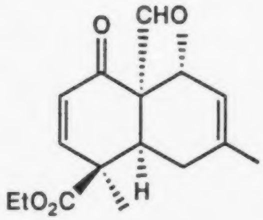
Dienone aldehyde **114** (55 mg, 0.26 mmol) was stirred with fused $ZnCl_2$ (110 mg, 0.79 mmol) and isoprene (excess) in dichloromethane under an argon atmosphere for 17 h. Work-up as usual followed by flash chromatography gave adducts **119** and **120**

(62 mg, 85% yield) in a ratio of 5:1 and recovered starting material (5 mg, 10% yield).

(1S*,5S*,6S*,10S*)-5-Carbethoxy-1-formyl-5,8,10-trimethylbicyclo[4.4.0]deca-3,8-dien-2-one (121) and (1S*,5S*,6S*,10R*)-5-carbethoxy-1-formyl-5,8,10-trimethylbicyclo[4.4.0]deca-3,8-dien-2-one (122)



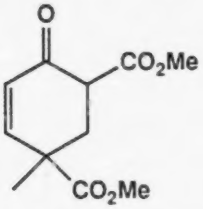
121



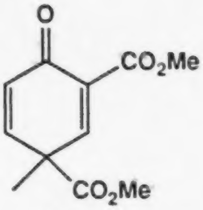
122

A solution of dienone aldehyde **114** (60 mg, 0.29 mmol) and (*E*)-2-methyl-1,3-pentadiene (236 mg, 2.88 mmol) in benzene (5 mL) was heated under reflux under argon for 8 h and cooled to room temperature. The volatiles were removed *in vacuo* and the residue was subjected to chromatography. Elution with ethyl acetate and hexane (15:85) gave two major adducts **121** and **122** (1:3 ratio, 77.8 mg, 93% yield) as colorless oil: ir ($CHCl_3$ cast) 1727 (C=O, ester and aldehyde), 1687 cm^{-1} (C=O, enone); ^1H nmr (200 MHz), for the minor isomer: δ 9.65 (s, 1 H), 6.86 (dd, J = 10, 2 Hz, 1 H), 5.95 (d, J = 10 Hz, 1 H), 5.26 (m, 1 H), 4.05-4.25 (m, 2 H), 3.02 (m, 1 H), 3.00 (ddd, J = 9, 7, 2 Hz, 1 H), 1.95-2.10 (m, 2 H), 1.61 (br s, 3 H), 1.45 (s, 3 H) and 1.23 (d, J = 7 Hz, 3 H); for the major isomer: δ 9.85 (s, 1 H), 6.80 (d, J = 10 Hz, 1 H), 6.00 (d, J = 10 Hz, 1 H), 4.05-4.25 (m, 2 H), 2.94 (dd, J = 6, 4.5 Hz, 1 H), 2.66 (m, 1 H), 1.95-2.10 (m, 2 H), 1.57 (br s, 3 H), 1.44 (s, 3 H) and 1.15 (d, J = 7 Hz, 3 H); hrms M^+ 190.1515 (calcd. for $C_{17}H_{22}O_4$: 290.1518).

4,6-Bis(carbomethoxy)-4-methyl-2-cyclohexenone (124) and 2,4-bis(carbomethoxy)-4-methyl-2,5-cylcohexadienone (123)



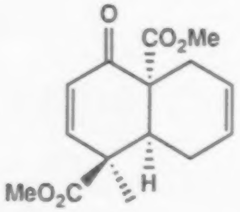
124



123

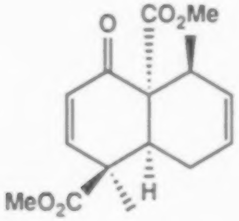
To a sloution of diisopropylamine (0.53 mL, 3.71 mmol) in THF (10 mL) at 0°C under an argon atmosphere, was added *n*-BuLi (1.43 mL, 2.5 M in hexane) dropwise. The solution was stirred at 0°C for 15 min and cooled to -78°C. Enone ester **112** (300 mg, 1.79 mmol) in THF (5 mL) was introduced dropwise over a period of 5 min. The mixture was allowed to warm up to 0°C for 30 min and cooled to -78°C again. HMPA (0.31 mL, 1.79 mmol) was added to the above solution followed by methyl cyanoformate (0.17 mL, 1.79 mmol). The mixture was stirred at -78°C for 30 min and warmed up quickly to 0°C. Saturated ammonium chloride (10 mL) was added and the mixture was extracted with ether (3 x 20 mL). The extracts were combined, washed with water and brine and dried over magnesium sulfate. Filtration and concentration gave the crude product which was subjected to chromatography. Elution with ethyl acetate and hexane (5:95) gave keto ester **124** (398 mg, 99% yield) as a light yellow oil: ^{1}H nmr (300 MHz) a mixture of three isomers: δ 11.85 (br s), 7.45 (dd, *J* = 10, 2 Hz), 6.79 (dd, *J* = 10, 2 Hz), 6.38 (d, *J* = 10 Hz), 6.25 (d, *J* = 10 Hz), 6.20 (d, *J* = 10 Hz), 5.98 (d, *J* = 10 Hz), 3.79 (s), 3.78 (s), 3.76 (s), 3.75 (s), 3.74 (s), 3.72 (s), 3.65 (dd, *J* = 14, 4.5 Hz), 3.54 (dd, *J* = 12, 5 Hz), 2.91 (d, *J* = 16 Hz), 2.78 (dd, *J* = 14, 12 Hz), 2.66 (ddd, *J* = 14, 5, 2 Hz), 2.55 (dd, *J* = 16, 1 Hz), 2.27 (t, *J* = 14 Hz, 2 H), 2.26 (dd, *J* = 14, 2 Hz), 1.49 (s), 1.48 (s), 1.30 (s); hrms M$^+$ 226.0843 (calcd. for $C_{11}H_{14}O_5$: 226.0841). Using the standard procedure, phenylselenenylation-oxidative elimination of keto ester **124** (368 mg, 1.63 mmol) gave dienone diester **123** (298 mg, 82% yield) as a colorless oil: ir (CH_2Cl_2 cast) 1736 (C=O, esters) and 1670 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz) δ 7.71 (d, *J* = 3 Hz, 1 H, -C**H**=C(CO)CO$_2$Me), 7.04 (dd, *J* = 10, 3 Hz, 1 H, -C**H**=CHCO), 6.35 (d, *J* = 10 Hz, 1 H, -CH=C**H**CO), 3.88 (s, 3 H), 3.78 (s, 3 H), 1.52 (s, 3 H); hrms M$^+$ 224.0686 (calcd for $C_{11}H_{12}O_5$: 224.0685).

(1R*,5S*,6S*)-1,5-Bis(carbomethoxy)-5-methylbicyclo[4.4.0]deca-3,8-dien-2-one (125)



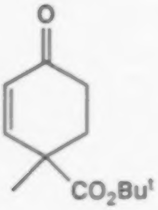
The procedure discussed previously for the preparation of adduct **118** from dienone aldehyde **114** was used for the reaction between dienone diester **123** (73 mg, 0.326 mmol) and 1,3-butadiene (saturated in dichloromethane) in the presence of $ZnCl_2$ (89 mg, 0.65 mmol) as a catalyst. The mixture was stirred at room temperature under an argon atmosphere for 16 h and worked up. Purification by chromatography gave adduct **125** (86 mg, 95% yield) as a colorless oil: ir ($CHCl_3$ cast) 1735 (C=O, esters) and 1688 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 6.73 (dd, J = 10, 0.5 Hz, 1 H, -**CH**=CHCO), 6.00 (d, J = 10 Hz, 1 H, -CH=**CH**CO), 5.59 (dm, J = 10 Hz, 1 H), 5.43 (dm, J = 10 Hz, 1 H), 3.68 (s, 3 H), 3.60 (s, 3 H), 2.97 (t, J = 6 Hz, 1 H), 2.63 (dm, J = 17.5 Hz, 1 H), 2.42 (dm, J = 17.5 Hz, 1 H), 2.17 (dm, J = 18 Hz, 1 H), 2.00 (dm, J = 18 Hz, 1 H) and 1.38 (s, 3 H); ^{13}C nmr (APT) δ 195.50 (p), 173.62 (p), 173.13 (p), 149.38 (a), 126.11 (a), 124.16 (a), 124.02 (a), 56.02 (p), 52.69 (a), 52.50 (a), 47.16 (p), 42.17 (a), 28.60 (p), 25.48 (a), 24.57 (p); hrms M^+ 278.1153 (calcd. for $C_{15}H_{18}O_5$: 278.1154).

(1R*,5S*,6S*,10S*)-1,5-Bis(carbomethoxy)-5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (126)



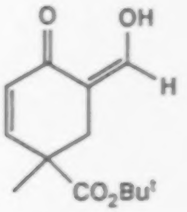
Dienone diester **123** (46 mg, 0.21 mmol) reacted with *trans*-piperylene (0.2 mL, 2.1 mmol) in dichloromethane using $ZnCl_2$ (56 mg, 0.41 mmol) as a catalyst at 0°C under argon for 4.5 h followed by flash chromatography to give adduct **126** (56 mg, 95% yield) as a colorless oil: ir ($CHCl_3$ cast) 1732 (C=O, esters) and 1693 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 6.77 (dd, *J* = 10, 2 Hz, 1 H, -C**H**=CHCO), 5.95 (d, *J* = 10 Hz, 1 H, -CH=C**H**CO), 5.54 (ddd, *J* = 10, 2, 2 Hz, 1 H), 5.39 (ddd, *J* = 10, 7, 3 Hz, 1 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.06 (ddd, *J* = 9, 7, 2 Hz, 1 H), 2.72 (m, 1 H), 2.12 (m, 1 H), 1.85 (m, 1 H), 1.36 (s, 3 H) and 1.25 (d, *J* = 7 Hz, 3 H); ^{13}C nmr (APT) δ 195.06 (p), 174.15 (p), 173.94 (p), 145.32 (a), 130.66 (a), 128.07 (a), 122.95 (a), 58.50 (p), 52.50 (a), 52.31 (a), 49.55 (p), 45.46 (a), 38.60 (a), 27.53 (p), 23.79 (a), 16.76 (a); hrms M^+ 292.1307 (calcd. for $C_{16}H_{20}O_5$: 292.1311).

4-(*t*-Butoxycarbonyl)-4-methyl-2-cyclohexenone (128)

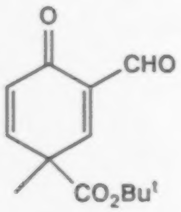


A high presure tube charged with *trans*-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (3.2 g, 90% pure, 16.9 mmol), *t*-butyl methacrylate (1.2 g, 8.45 mmol) and a few crystals of DNB in benzene (3 mL) was cooled to -196°C, deoxygenated under high vacuum (5 micron) and sealed. The tube was warmed up slowly to room temperature, put into a 90°C oil bath for 2 days and then cooled to room temperature. The volatiles were removed in *vacuo* and the residue was dissloved in 0.001 N HCl-THF (1:4, 15 mL) and stirred for 1 h. The THF was mostly removed *in vacuo* and the remaining mixture was diluted with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The extracts were combined, washed with water and dried over magnesium sulfate. Filtration and concentration gave the crude product which was purified by chromatography. Elution with ethyl acetate and hexane (10:90) gave enone ester **128** (470 mg, 27% yield) as a colorless oil: ir ($CHCl_3$ cast) 1726 (C=O, ester) and 1688 cm^{-1} (C=O, enone); ^{1}H nmr (80 MHz) δ 6.85 (d, J = 10 Hz, 1 H), 5.90 (d, J = 10 Hz, 1 H), 1.70-2.60 (m, 4 H), 1.45 (s, 9 H) and 1.40 (s, 3 H); hrms m/z 210.1245 (M$^+$, calcd. for $C_{12}H_{18}O_4$: 210.1256), 109.0653 (M$^+$-$CO_2{}^tBu$, calcd. for C_7H_9O: 109.0653).

4-(*t*-Butoxycarbonyl)-6-formyl-4-methyl-2-cyclohexenone (129) and 4-(*t*-butoxycarbonyl)-2-formyl-4-methyl-2,5-cyclohexadienone (127)



129

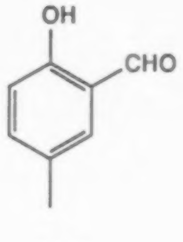


127

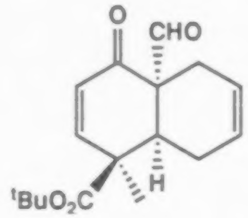
The same formylation process used for **112** was applied to the formylation of enone ester **128** (210 mg, 0.1 mmol) with sodium hydride (80 mg, 60% oil dispersion, 0.2 mmol) and ethyl formate (5.3 mL, 6.6 mmol) to give compound **129** (0.23 g) as a yellowish oil: ir ($CHCl_3$ cast) 1728 (C=O, ester), 1689 (C=O, enone), 1650 and 1578 cm^{-1} (C=C, enol); ^{1}H nmr (80 MHz) δ 13.60 (br s, 1 H), 7.55

(br s, 1 H), 6.80 (d, *J* = 10 Hz, 1 H), 6.00 (d, *J* = 10 Hz, 1 H), 2.90 (d, *J* = 14 Hz, 1 H), 2.40 (d, *J* = 10 Hz, 1 H), 1.45 (s, 9 H) and 1.30 (s, 3 H); hrms M+ 238.1209 (calcd. for $C_{13}H_{18}O_4$: 238.1205). Without purification, the above crude product was directly subjected to phenylselenenylation-oxidative elimination. After chromatography, dienone aldehyde **127** (0.21 g, 89% yield) was obtained as a light yellow oil: ir ($CHCl_3$ cast) 1716 (C=O, ester), 1704 (C=O, aldehyde) and 1674 cm^{-1} (C=O, enone); ^1H nmr (80 MHz) δ 10.20 (s, 1 H, -C**H**O), 7.70 (d, *J* = 3 Hz, 1 H, -C**H**=C(CO)CHO), 7.05 (dd, *J* = 10, 3 Hz, 1 H, -C**H**=CHCO), 6.30 (d, *J* = 10 Hz, 1 H, -CH=C**H**CO), 1.60 (s, 3 H) and 1.49 (s, 9 H); hrms m/z 221.0815 (M^+-CH_3, calcd. for $C_{12}H_{13}O_4$: 221.0814) and 135.0448 (M^+-CO^{t}Bu, calcd. for $C_8H_7O_2$: 135.0446).

2-Hydroxy-5-methylbenzaldehyde (130) and (1S*,5S*,6S*)-5-(t-butoxycarbonyl)-1-formyl-5-methylbicyclo[4.4.0]deca-3,8-dien-2-one (131)



130



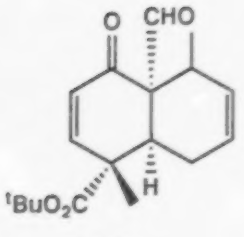
131

Dienone ester **127** (26 mg, 0.11 mmol) was reacted with 1,3-butadiene (saturated in dichloromethane) using $ZnCl_2$ (45 mg, 0.33 mmol) as catalyst for 6.5 h at 0°C under an argon atmosphere.

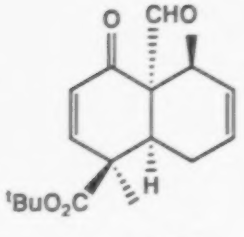
Work-up as usual followed by purification by chromatography using ethyl acetate and hexane (5:95) gave the aromatization product **130** (9 mg, 60% yield): ^{1}H nmr (300 MHz) δ 10.82 (s, 1H), 9.85 (s, 1 H), 7.35 (m, 2 H), 6.90 (d, J = 9 Hz, 1 H) and 2.31 (s, 3 H); ^{13}C nmr (APT) δ 196.59 (a), 159.63 (p), 138.07* (a), 136.00 (p), 133.44 (a), 129.18 (p), 117.46 (a), 20.27 (a).

Further elution gave adduct **131** (8 mg, 25% yield) as a colorless oil: ir ($CHCl_3$ cast) 1728 (C=O, ester and aldehyde) and 1681 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz) δ 9.62 (s, 1 H, -C**H**O), 6.86 (dd, *J* = 10, 0.5 Hz, 1 H, -C**H**=CHCO), 6.02 (d, *J* = 10 Hz, 1 H, -CH=C**H**CO), 5.68 (m, 1 H), 5.59 (m, 1 H), 2.88 (dd, *J* = 6, 6 Hz, 1 H), 2.69 (dm, *J* = 18 Hz, 1 H), 2.32 (dm, *J* = 18 Hz, 1 H), 2.22 (m, 2 H), 1.47 (s, 9 H) and 1.44 (s, 3 H); ^{13}C nmr (APT) δ 200.38 (a), 196.53 (p), 171.99 (p), 151.14 (a), 126.24 (a), 126.13 (a), 122.63 (a), 82.46 (p), 59.96 (p), 47.94 (p), 40.00 (a), 27.92 (a), 26.58 (a), 26.05 (p), 23.94 (p); hrms $[M-CO_2{}^tBu]^+$ 160.0878 (calcd. for $C_{11}H_{12}O$: 160.0888).

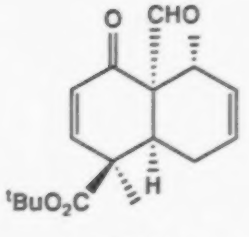
(1S*,5R*,6S*)-5-(*t*-Butoxycarbonyl)-1-formyl-5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (131), (1S*,5S*,6S*,10S*)-5-(*t*-butoxycarbonyl)-1-formyl-5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (132) and (1S*,5S*,6S*,10R*)-5-(*t*-butoxycarbonyl)-1-formyl-5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (133)



132



133

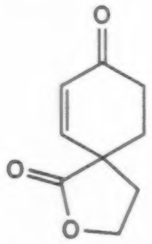


134

A solution of dienone aldehyde **127** (84 mg, 0.36 mmol) and *trans*-piperylene (0.36 mL, 3.6 mmol) in benzene (5 mL) was heated to reflux under an argon atmosphere for 36 h and cooled to room temperature. The volatiles were removed *in vacuo* and the residue was subjected to chromatography. Elution with ethyl acetate and hexane (5:95) first gave adduct **132** (4.3 mg, 4% yield) as a yellowish oil: ^{1}H nmr (300 MHz) δ 9.50 (s, 1 H, -C**H**O), 6.45 (dd, J = 10, 2 Hz, 1 H, -C**H**=CHCO), 5.95 (d, J = 10 Hz, 1 H, -CH=C**H**CO), 3.30 (ddd, J = 9.5, 6.5, 2 Hz, 1 H), 2.80 (m, 1 H), 2.27 (m, 1 H), 1.96 (m, 1 H), 1.45 (s, 9 H), 1.33 (s, 3 H) and 1.30 (d, J = 7 Hz, 3 H). Continued elution gave a mixture of adducts **132**, **133** and **134** (4.3 mg).

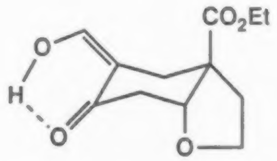
Further elution gave adduct **133** and **134** (86.7 mg, 80% yield) as a yellowish oil which solidified on standing in the freezer: m.p. 68-76°C; ir ($CHCl_3$ cast) 1722 (C=O, ester and aldehyde) and 1689 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz) two isomers in a ratio of 3.43:1; for the major isomer: δ 9.67 (s, 1 H, -C**H**O), 6.82 (dd, J = 10, 2 Hz, 1 H, -C**H**=CHCO), 5.95 (d, J = 10 Hz, 1 H, -CH=C**H**CO), 5.59 (ddd, J = 10, 4, 2 Hz, 1 H), 5.51 (ddd, J = 10, 7, 3 Hz, 1 H), 2.96 (ddd, J = 9.5, 7, 2 Hz, 1 H), 2.69 (m, 1 H), 2.29 (m, 1 H), 2.06 (m, 1 H), 1.49 (s, 9 H), 1.42 (s, 3 H) and 1.28 (d, J = 7 Hz, 3 H); for the minor isomer: δ 9.84 (s, 1 H, -C**H**O), 6.86 (dd, J = 10, 1 Hz, 1 H, -C**H**=CHCO), 5.98 (d, J = 10 Hz, 1 H, -CH=C**H**CO), 5.63 (m, 1 H), 5.56 (m, 1 H), 3.10 (m, 1 H), 2.99 (t, J = 6 Hz), 2.30 (m, 1 H), 2.24 (m, 1 H), 1.48 (s, 9 H), 1.41 (s, 3 H) and 1.17 (d, J = 7 Hz, 3 H); hrms M+ 304.1692 (calcd. for $C_{18}H_{24}O_4$: 304.1675). Anal. calcd. for $C_{18}H_{24}O_4$: C 71.03, H 7.95; found: C 70.83, H 7.76. Further elution gave the recovered starting enone aldehyde (6.7 mg, 8% yield).

4-Carboxy-4-(2-hydroxyethyl)-2-cyclohexenone γ-lactone (139)



A solution of *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (0.9 g, 90% pure, 4.49 mmol), α-methylenebutyrolactone (0.22 g, 2.25 mmol) and a few crystals of DNB in benzene (6 mL) was heated to reflux under an argon atmosphere for 60 h and cooled to room temperature. The volatiles were removed *in vacuo* and the residue was dissolved in THF-0.001 N HCl (4:1, 10 mL) and stirred for 1 h. Water was added to the mixture and the organic solvent was evaporated in *vacuo*. The remaining aqueous solution was extracted with dichloromethane (3 x 10 mL). The extracts were combined, washed with water and dried over magnesium sulfate. Filtration and concentration gave the crude product which was purified by chromatography. Elution with ethyl acetate and hexane (40:60) gave compound **139** (0.24 g, 65% yield) as a light yellow solid. Recrystallization from ether and petroleum ether gave a white rhombic crystal (m.p. 79-80°C): ir ($CHCl_3$ cast) 1750 (C=O, lactone) and 1679 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz) δ 6.67 (d, J = 10 Hz, 1 H, -C**H**=CHCO), 6.16 (d, J = 10 Hz, 1 H, -CH=C**H**CO), 4.45 (m, 2 H, -C**H**$_2$O-), 2.86(m, 1 H), 2.34-2.51 (m, 4 H) and 2.15 (m, 1 H); hrms M$^+$ 166.0632 (calcd. for $C_9H_{10}O_3$: 166.0630).

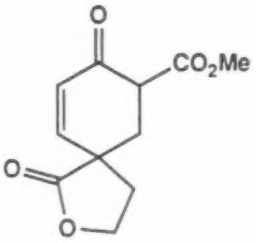
(1S*,6R*)-1-Carbethoxy-3-formyl-7-oxabicyclo[4.3.0]nonan-4-one (140)



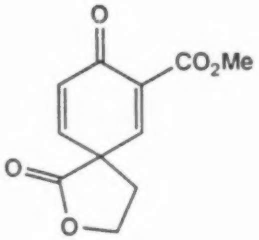
When lactone **139** (100 mg, 0.60 mmol) was subjected to the formylation conditions described previously (NaH: 50 mg, 60% oil dispersion, 1.2 mmol; ethyl formate: 3.2 mL, 39.7 mmol), compound **140** (50 mg, 43% yield) was obtained after flash chromatography using ethyl acetate and hexane (30:70) as an eluent. For **140**, ir ($CHCl_3$ cast) 2600-3600 (br, OH), 1727 (C=O, ester), 1662 and 1597 cm^{-1} (β-hydroxy enone); ^{1}H nmr (300 MHz) δ 13.60 (br s, 1 H), 7.49 (s, 1 H), 4.48 (dd, J = 4.5, 3.5 Hz, 1 H), 4.21 (q, J = 7 Hz, 2 H), 3.91 (ddd, J = 9, 8, 2.5 Hz, 1 H), 3.64

(ddd, J = 10, 9, 6 Hz, 1 H), 2.77 (dd, J = 15, 1 Hz, 1 H), 2.72 (dd, J = 16.5, 3.5 Hz, 1 H), 2.64 (dd, J = 16.5, 4.5 Hz, 1 H), 2.43 (ddd, J = 13, 6, 2.5 Hz, 1 H), 2.34 (d, J = 15 Hz, 1 H), 1.85 (ddd, J = 13, 10, 8 Hz, 1 H) and 1,28 (t, J = 7 Hz, 3 H); hrms M^+ 240.1002 (calcd. for $C_{12}H_{16}O_5$: 240.0998).

6-Carbomethoxy-4-carboxy-4-(2-hydroxyethyl)-2-cyclohexenone γ-lactone (143) and 2-carbomethoxy-4-carboxy-4-(2-hydroxyethyl)-2,5-cyclohexadienone γ-lactone (142)



143

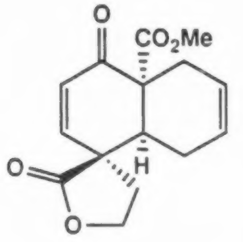


142

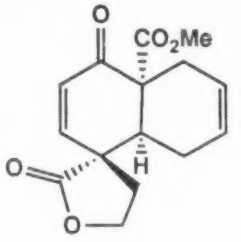
To a solution of diisopropylamine (0.53 mL, 3.8 mmol) in THF (10 mL) at 0°C under an argon atmosphere, was added *n*-BuLi (1.45 mL, 2.5 M in hexane). The mixture was stirred at 0°C for 15 min and cooled to -78°C. Lactone **139** (300 mg, 1.81 mmol) in THF (5 mL) was added to the above LDA solution dropwise over a period of 5 min. The resulting mixture was warmed up to 0°C for 30 min and cooled to -78°C again. HMPA (0.32 mL, 1.81 mmol) was added followed by methyl cyanoformate (0.17 mL, 2.17 mmol). The mixture was then stirred at -78°C for 1 h and warmed up quickly to 0°C. Saturated ammonium chloride (10 mL) was added and the mixture extracted with ether (3 x 10 mL). The extracts were combined, washed with water and brine, and dried over magnesium sulfate. Filtration and concentration gave the crude product which was subjected to flash chromatography. Elution with ethyl acetate and hexane (40:60) gave keto ester **143** (364 mg, 90% yield) as a light yellow oil: ir ($CHCl_3$ cast) 1765 (C=O, lactone), 1742 (C=O, ester), 1684 (C=O, enone), 1625 and 1597 cm^{-1} (enol); ^1H nmr (300 MHz) two isomers in a ratio of 2.5:1; for the major isomer: δ 11.85 (br s, 1 H), 6.04 (dd, J = 10, 1.5 Hz, 1 H), 6.15 (m, 1 H), 4.30-4.47 (m, 2 H), 3.77 (s, 3 H), 2.82 (d, J = 15 Hz, 1 H), 2.66 (d, J = 15 Hz, 1 H), 2.12-2.57 (m); for the minor isomer: δ 6.74 (dd, J = 10, 2 Hz, 1 H), 6.19 (m, 1 H), 4.13 (m, 2 H), 3.50 (dd, J = 13.5, 5 Hz, 1 H), 2.12-2.57 (m); hrms M^+ 224.0687 (calcd. for $C_{11}H_{12}O_5$: 224.0685).

Under the standard procedure for the phenylselenenylation-oxidative elimination, compound **143** (428 mg, 1.91 mmol) gave dienone lactone **142** (200 mg, 47% yield) as a white solid plus recovered starting keto ester **143** (214 mg, 45%). Recrystallization of **142** from dichloromethane and pentane gave hexagonal crystals (m.p. 127.5-128.5°C): ir (CH_2Cl_2 cast) 1768 (C=O, lactone), 1741 (C=O, ester) and 1669 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 7.50 (d, J = 3 Hz, 1 H, -C**H**=C(CO)CO_2Me), 6.82 (dd, J = 10, 3 Hz, 1 H, -C**H**=CHCO), 6.53 (d, J = 10 Hz, 1 H, -CH=C**H**CO), 4.62 (t, J = 7 Hz, 1 H), 4.61 (t, J = 7 Hz, 1 H), 3.88 (s, 3 H) and 2.60-2.75 (m, 2 H); hrms m/z 191.0347 (M^+-OMe, calcd. for $C_{10}H_7O_4$: 191.0344); cims $[M+NH_4]^+$ 240.

(1R*,5S*,6S*)-1-Carbomethoxy-5-carboxy-5-(2-hydroxyethyl)-bicyclo[4.4.0]deca-3,8-dien-2-one γ-lactone (144) and (1R*,5R*,6S*)-1-carbomethoxy-5-carboxy-5-(2-hydroxyethyl)-bicyclo[4.4.0]deca-3,8-dien-2-one γ-lactone (145)



144



145

Using the same procedure for the addition of **114** with 1,3-butadiene, dienone lactone **142** (81 mg, 0.36 mmol) was treated with 1,3-butadiene (saturated in dichloromethane) and $ZnCl_2$ (99 mg, 0.72 mmol) at room temperature for 15 h under argon. Work-up as usual followed by flash chromatography using ethyl acetate and hexane (40:60) as an eluent gave adduct **144** (38 mg, 38% yield) as a white solid. Recrstallization from dichloromethane and pentane gave a white powder (m.p. 160-161°C): ir (CH_2Cl_2 cast) 1768 (C=O, lactone), 1728 (C=O, ester) and 1692 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz) δ 6.45 (dd, *J* = 10, 2 Hz, 1 H, -C**H**=CHCO), 6.24 (d, *J* = 10 Hz, 1 H, -CH=C**H**CO), 5.68 (dm, *J* = 10 Hz, 1 H), 5.56 (dm, *J* = 10 Hz, 1 H), 4.39-4.45 (m, 2 H), 3.13 (ddd, *J* = 9, 7, 2 Hz, 1 H), 3.01 (dm, *J* = 17 Hz, 1 H), 2.56 (ddd, *J* = 13.5, 5, 3 Hz, 1 H), 2.27-2.42 (m, 3 H) and 2.16 (m, 1 H); ^{13}C nmr (APT) δ 193.39 (p), 175.82 (p), 174.23 (p), 144.32 (a), 129.99 (a), 123.57

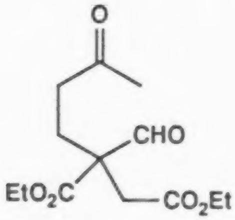
(a), 123.43 (a), 65.81 (p), 55.77 (p), 53.00 (a), 49.04 (p), 38.15 (a), 34.54 (p), 29.91 (p) and 25.75 (p); hrms M^+ 276.0997 (calcd. for $C_{15}H_{16}O_5$: 276.0998).

Further elution gave adduct **145** (47 mg, 47%) as a white solid. Recrystallization from dichloromethane and pentane gave a hexagonal crystal (m.p. 234.5-236°C): ir (CH_2Cl_2 cast) 1753 (C=O, lactone), 1737 (C=O, ester) and 1676 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 6.73 (d, J = 10 Hz, 1 H, -C**H**=CHCO), 6.12 (d, J = 10 Hz, 1 H, -CH=C**H**CO), 5.83 (dm, J = 10 Hz, 1 H), 5.71 (dm, J = 10 Hz, 1 H), 4.32-4.44 (m, 2 H), 3.74 (s, 3 H, -OC**H**$_3$), 3.63 (br d, J = 7 Hz, 1 H), 2.81 (dt, J = 13, 9 Hz, 1 H), 2.78 (dm, J = 18 Hz, 1 H), 2.31 (dm, J = 19 Hz, 1 H), 2.22 (ddd, J = 13, 6, 3.5 Hz, 1 H), 2.05 (dm, J = 18 Hz, 1 H) and 1.75 (dm, J = 19 Hz, 1 H); ^{13}C nmr (APT) δ 195.59 (p), 176.88 (p), 170.90 (p), 144.93 (a), 127.31 (a), 125.52 (a), 124.96 (a), 65.13 (p), 56.50 (p), 52.86 (a), 49.05 (p), 35.91 (a), 30.78 (p), 27.64 (p) and 25.25 (p); hrms M^+ 276.0996 (calcd. for $C_{15}H_{16}O_5$: 276.0998); cims $[M+NH_4]^+$ 294.

Diethyl formylsuccinate (150)

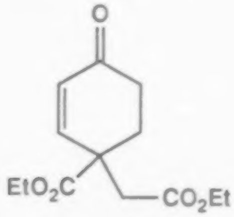
To a suspension of sodium hydride (9.6 g, 60% dispersion in oil, 0.24 mol) in THF (50 mL) at 0°C under an argon atmosphere, was added ethyl formate (32 mL, 0.4 mol). The mixture was stirred for 1 h and diethyl succinate (34.8 g, 0.2 mol) in THF (40 mL) was added dropwise over a period of 30 min followed by a few drops of ethanol. The mixture was then stirred at room temperature overnight and cooled to 0°C. Ice-cold 1 N HCl was added until the solution was acidic (pH~4). The mixture was extracted with ether (3 x 120 mL). The extracts were combined, washed with water and brine, and dried over magnesium sulfate. Filtration and concentration gave the crude product which was distilled at 110°C/2.8 torr to give diethyl formylsuccinate (29 g, 71% yield) as a colorless oil: ir ($CHCl_3$ cast) 1721 (C=O, ester); ^1H nmr (80 MHz) two isomers; for the major isomer: δ 11.55 (d, *J* = 12 Hz, 1 H), 7.10 (d, *J* = 12 Hz, 1 H), 4.25 (m, 4 H), 3.10 (s, 2 H) and 1.30 (m, 6 H); for the minor isomer: δ 9.90 (s, 1 H), 4.25 (m, 4 H), 3.80 (t, *J* = 6 Hz, 1 H), 2.95 (d, *J* = 6 Hz, 2 H) and 1.30 (m, 6 H).

Ethyl 3-carbethoxy-3-formyl-6-oxo-heptanoate (151)



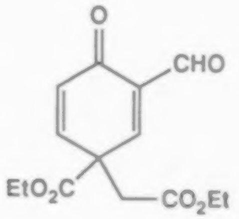
A solution of compound **150** (8.2 g, 40.6 mmol) , freshly distilled methyl vinyl ketone (4.1 mL, 48.7 mmol) and DABCO (5.5 g, 48.7 mmol) in THF (100 mL) was stirred at room temperature under an argon atmosphere for 2 days and diluted with ether (150 mL). The mixture was washed with ice-cold 1 N HCl (3 x 50 mL), water (50 mL) and brine. After being dried over magnesium sulfate, the mixture was filtered and concentrated to give Michael adduct **151** (11 g, ca. 100% yield) as a light yellow oil: ^{1}H nmr (300 MHz) δ 10.05 (s, 1 H), 4.28 (m, 2 H), 4.10 (q, *J* = 7 Hz, 2 H), 2.86 (d, *J* = 8.5 Hz, 2 H), 2.45 (t, *J* = 7.5 Hz, 2 H), 2.20 (s, 3 H), 1.98-2.10 (m, 2 H) and 1.21-1.36 (m, 6 H).

4-Carbethoxy-4-(carbethoxymethyl)-2-cyclohexenone (152)



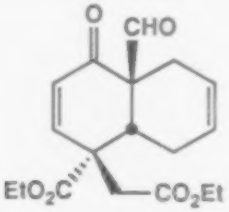
A solution of the crude product from preceeding experiment and *p*-TsOH (0.7 g, 4 mmol) in benzene (150 mL) was heated to reflux under an argon atmosphere with azeotropic removal of water. After being cooled to room temperature, the mixture was washed with half saturated sodium bicarbonate (2 x 50 mL) and water (50 mL), and dried over magnesium sulfate. Filtration and concentration gave the crude product. Bulb-to-bulb distillation at 110-115°C/0.4 torr gave product **152** (9.0 g, 85% yield) as a colorless oil: ir ($CHCl_3$ cast) 1727 (C=O, esters) and 1668 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz) δ 7.10 (d, *J* = 10 Hz, 1 H), 6.03 (d, *J* = 10 Hz, 1 H), 4.22 (q, *J* = 7 Hz, 2 H), 4.16 (q, *J* = 7 Hz, 2 H), 2.90 (d, *J* = 16 Hz, 1 H), 2.77 (d, *J* = 16 Hz, 1 H), 2.59 (m, 1 H), 2.40-2.50 (m, 2 H), 2.08 (m, 1 H), 1.30 (t, *J* = 7 Hz, 3 H) and 1.28 (t, *J* = 7 Hz, 3 H).

4-Carbethoxy-4-(carbethoxymethyl)-6-formyl-2-cyclohexenone and 4-carbethoxy-4-(carbethoxymethyl)-2-formyl-2,5-cyclohexadienone (149)



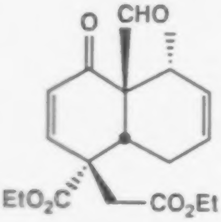
Formylation of **152** (2.54 g, 10 mmol) using the standard conditions (NaH: 0.8 g, 20 mmol, ethyl formate: 3.3 mL, 40 mmol) gave the corresponding α-formyl ketone (2.8 g): ^{1}H nmr (80 MHz) δ 7.60 (s, 1 H), 6.95 (d, *J* = 10 Hz, 1 H), 6.15 (d, *J* = 10 Hz, 1 H), 4.00-4.40 (m, 4 H), 2.90 (d, *J* = 14 Hz, 1 H), 2.50 (d, *J* = 14 Hz, 1 H), 1.30 (t, *J* = 7 Hz, 3 H) and 1.25 (t, *J* = 7 Hz, 3 H). Phenylselenenylation-oxidative elimination of the crude product gave dienone aldehyde **149** (1.4 g, 50% yield) as a yellowish flaky solid which was recrystallized from ether and petroleum ether: m.p. 87-88°C; ir ($CHCl_3$ cast) 1736 (C=O, esters), 1708 (C=O, aldehyde) and 1670 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz) δ 7.81 (d, *J* = 3 Hz, 1 H), 7.11 (dd, *J* = 10, 3 Hz, 1 H), 6.47 (d, *J* = 10 Hz, 1 H), 4.23 (qd, *J* = 7, 0.7 Hz, 2 H), 4.18 (q, *J* = 7 Hz, 2 H), 2.98 (d, *J* = 16.5 Hz, 1 H), 1.89 (d, *J* = 16.5 Hz, 1 H), 1.27 (t, *J* = 7 Hz, 3 H) and 1.25 (t, *J* = 7 Hz, 3 H); hrms m/z 235.0607 (M$^+$-OEt, calcd. for $C_{12}H_{11}O_5$: 235.0606), 207.0647 (base peak, M$^+$-CO_2Et, calcd. for $C_{11}H_{11}O_4$: 207.0657); cims [M+NH_4]$^+$ 298. Anal. calcd. for $C_{14}H_{16}O_6$: C 60.00, H 5.75; found: C 60.19, H 5.90.

(1R*,5R*,6R*)-5-Carbethoxy-5-(carbethoxymethyl)-1-formylbicyclo[4.4.0]deca-3,8-dien-2-one (153)



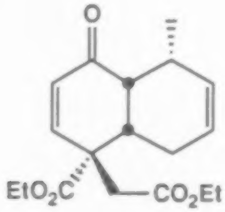
Using the same procedure for the transformation of **114** to **118**, dienone aldehyde **149** (56 mg, 0.2 mmol) was treated with 1,3-butadiene (saturated in dichloromethane) and ZnCl$_2$ (82 mg, 0.6 mmol) at room temperature under argon for 18 h. The usual work-up gave the crude product which was purified by chromatography. Elution with ethyl acetate and hexane (15:85) gave adduct **153** (56.6 mg, 84% yield) as a yellowish oil: ir (CHCl$_3$ cast) 1732 (C=O, esters and aldehyde) and 1672 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz) δ 9.61 (s, 1 H, -C**H**O), 7.22 (d, J = 10 Hz, 1 H, -C**H**=CHCO), 6.10 (d, J = 10 Hz, 1 H, -CH=C**H**CO), 5.67 (dm, J = 10 Hz, 1 H), 5.54 (dm, J = 10 Hz, 1 H), 3.27 (d, J = 17 Hz, 1 H), 2.86 (dd, J = 8, 3.5 Hz, 1 H), 2.68 (d quintet, J = 18, 2 Hz, 1 H), 2.47 (d, J = 17 Hz, 1 H), 2.48 (dm, J = 18 Hz, 1 H), 2.41 (dm, J = 19 Hz, 1 H), 2.10 (dm, J = 19 Hz, 1 H), 1.26 (t, J = 7 Hz, 3 H) and 1.25 (t, J = 7 Hz, 3 H); ^{13}C nmr (APT) δ 200.67 (a), 197.13 (p), 171.28 (p), 170.20 (p), 148.95 (a), 127.45 (a), 125.74 (a), 123.03 (a), 62.05 (p), 61.12(p), 58.79 (p), 47.67 (p), 43.34 (p), 37.95 (a), 26.33 (p), 22.62 (p), 14.14 (a) and 13.83 (a); hrms M$^+$ 334.1420 (calcd. for C$_{18}$H$_{22}$O$_6$: 334.1416).

(1R*,5R*,6R*,10R*)-5-Carbethoxy-5-(carbethoxymethyl)-1-formyl-10-methylbicyclo[4.4.0]deca-3,8-dien-2-one (154)



Dienone aldehyde **149** (104 mg, 0.36 mmol) was reacted with *trans*-piperylene (0.36 mL, 3.6 mmol) using $ZnCl_2$ (146 mg, 1.08 mmol) as a catalyst in dichloromethane at 0°C under an argon atmosphere for 3 h. Work-up as usual gave the crude product which was purified by chromatography. Elution with ethyl acetate and hexane (15:85) gave adduct **154** (107 mg, 83% yield) as a yellowish oil: ir ($CHCl_3$ cast) 1737 (C=O, esters and aldehyde) and 1691 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz) δ 9.69 (s, 1 H, -C**H**O), 7.09 (dd, *J* = 10, 2 Hz, 1 H, -C**H**=CHCO), 6.05 (d, *J* = 10 Hz, 1 H, -CH=C**H**CO), 5.58 (ddd, *J* = 10, 4, 2 Hz, 1 H), 5.49 (ddd, *J* = 10, 7, 3 Hz, 1 H), 4.21 (q, *J* = 7 Hz, 2 H), 4.12 (qd, *J* = 7, 0.5 Hz, 2 H), 3.10 (d, *J* = 16.5 Hz, 1 H), 2.96 (ddd, *J* = 9, 7, 2 Hz, 1 H), 2.74 (m, 1 H), 2.64 (d, *J* = 16.5 Hz, 1 H), 2.20 (m, 1 H), 2.05 (m, 1 H), 1.30 (t, *J* = 7 Hz, 3 H), 1.28 (d, *J* = 7 Hz, 3 H) and 1.25 (t, *J* = 7 Hz, 3 H); ^{13}C nmr (APT) δ 201.30 (a), 196.01 (p), 172.02 (p), 169.79 (p), 145.31 (a), 129.55 (a), 129.19 (a), 123.35 (a), 64.20 (p), 61.77 (p), 61.22 (p), 49.64 (p), 43.50 (p), 42.83 (a), 33.61 (a), 25.19 (p), 16.69 (a), 14.10 (a) and 13.98 (a); hrms M+ 348.1576 (calcd. for $C_{19}H_{24}O_6$: 348.1573).

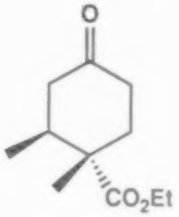
(1R*,5R*,6R*,10R*)-5-Carbethoxy-5-(carbethoxymethyl)-10-methylbicyclo[4.4.0]deca-3,8-dien-2-one (155)



A solution of adduct **154** (80 mg) in ethanol in the presence of a trace amount of sodium hydride was stirred at room temperature overnight and concentrated. The residue was subjected to chromatography. Elution with ethyl acetate and haxane (5:95) gave compound **155** as a white solid. Recrystallization from ethanol and water gave a needle like crystal (m.p. 84.5-86.5°C): ir ($CHCl_3$ cast) 1735 (C=O, esters) and 1690 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 7.01 (dd, J = 10.5, 2 Hz, 1 H), 5.89 (d, J = 10.5 Hz, 1 H), 5.59 (dm, J = 10 Hz, 1 H), 5.44 (dddd, J = 10, 4.5, 2.5, 2.5 Hz, 1 H), 4.24 (m, 2 H), 4.15 (q, J = 7 Hz, 2 H), 3.20 (d, J = 16 Hz, 1 H), 3.02 (d, J = 16 Hz, 1 H), 2.85 (ddd, J = 3.5, 3.5, 0.5 Hz, 1 H), 2.53 (dddd, J = 12, 6, 3.5, 2 Hz, 1 H), 2.43 (m, 1 H), 2.08 (dddd, J = 18, 12, 4, 2 Hz, 1 H), 1.81 (dm, J = 18 Hz, 1 H), 1.42 (d, J = 7.5 Hz, 3 H), 1.30 (t, J = 7 Hz, 3 H) and 1.26 (t, J = 7 Hz, 3 H); ^{13}C nmr (APT) δ 198.88 (p), 172.80 (p), 170.36 (p), 144.49 (a), 131.66 (a), 129.25 (a), 123.18 (a), 61.47 (p), 61.07 (p), 49.93 (p), 47.31

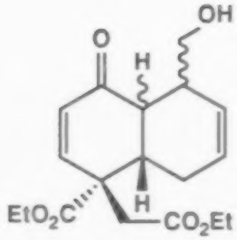
(a), 45.11 (a), 42.03 (p), 34.01 (a), 24.80 (p), 16.94 (a) and 14.16 (a); hrms M+ 320.1620 (calcd. for $C_{18}H_{24}O_5$: 320.1624). Anal. calcd. for $C_{18}H_{24}O_5$: C 67.48, H 7.55; found: C 67.09, H 7.56.

(3S*,4S*)-4-Carbethoxy-3,4-dimethylcyclohexanone (157)



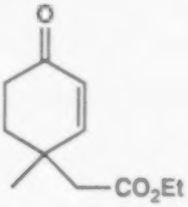
A mixture of enone ester **90** (1.0 g, 5.1 mmol) and Pd/C (0.005% catalyst by weight) in ethyl acetate (40 mL) was purged twice with hydrogen gas and the mixture was shaken under 25 p.s.i of hydrogen for 4 h. Filtration and concentration gave the crude product. Purification by chromatography using ethyl acetate and hexane (5:95) gave compound **157** (0.87g, 86% yield) as a colorless oil: ir ($CHCl_3$ cast) 1719 cm^{-1} (C=O, ester and ketone); ^1H nmr (300 MHz) a mixture of two isomers in a ratio of 11:1; for the major isomer: δ 4.20 (q, J = 7 Hz, 2 H), 2.25-2.60 (m, 5 H), 2.00 (m, 1 H), 1.73 (m, 1 H), 1.36 (s, 3 H), 1.29 (t, J = 7 Hz, 3 H) and 1.03 (d, J = 7 Hz, 3 H); hrms M+ 198.1250 (calcd. for $C_{11}H_{18}O_3$: 198.1256).

(5S*,6S*)-5-Carbethoxy-5-(carbethoxymethyl)-10-(hydroxymethyl)bicyclo[4.4.0]dec-3,8-dien-2-one



Dienone aldehyde **149** (100 mg, 0.36 mmol) was treated with 5-hydroxy-1,3-pentadiene (45 mg, 0.54 mmol) and $ZnCl_2$ (97 mg, 0.71 mmol) in dichloromethane at 0°C for 5 min. Work-up as usual followed by chromatography gave adduct **162** (73 mg, 62% yield) as a yellowish oil: ir (CH_2Cl_2 cast) 3420 (br, OH), 1730 (C=O, esters) and 1679 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 7.15 (dd, J = 10, 2 Hz, 1 H), 5.94 (d, J = 10 Hz, 1 H), 5.83 (ddd, J = 10, 4, 2 Hz, 1 H), 5.41 (ddd, J = 10, 6, 3 Hz, 1 H), 5.33 (br d, J = 2.5 Hz, 1 H), 4.07-4.29 (m, 6 H), 3.49 (br s, 1 H), 3.33 (d, J = 17 Hz, 1 H), 3.21 (m, 1 H), 2.92 (d, J = 17 Hz, 1 H), 2.92 (m, 1 H), 2.03-2.26 (m, 2 H), 1.38 (t, J = 7 Hz, 3 H) and 1.27 (t, J = 7 Hz, 3 H); hrms M^+ 336.1569 (calcd. for $C_{18}H_{24}O_6$: 336.1573).

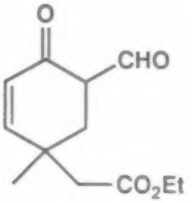
4-Carbethoxymethyl-4-methyl-2-cyclohexenone (165)



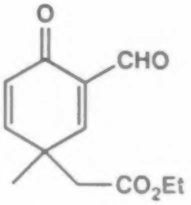
To a solution of anisole (10 g, 75.8 mmol) in THF (10 mL), absolute ethanol (20 mL) and liquid ammonia (60 mL) at -78°C under an argon atmosphere, were added small pieces of lithium metal (1.2 g, 171 mmol) at a rate sufficient to maintain a blue color for a period of 30 min. Then ammonium chloride (15 g) was added and the mixture was allowed to warm up to room temperature, allowing the ammonia to evaporate. Cold water (100 mL) was then added to the residue and the mixture was extracted with ether (3 x 100 mL). The extracts were combined, washed with brine and dried over magnesium sulfate. Filtration and concentration gave the crude reduction product (10 g, ~95% pure) as a colorless oil: ^{1}H nmr (80 MHz) δ 5.40 (br s, 1 H), 4.65 (br s, 1 H), 3.60 (s, 3 H), 2.75 (s, 4 H) and 1.75 (s, 3 H). To the crude product dissolved in ether (80 mL), were added dry methanol (13 mL) and a few crystals of *p*-TsOH. The mixture was allowed to stand at room temperature for 8 h and finally heated to reflux under an argon atmosphere for 8 h. After being cooled down to room temperature, the mixture was washed with half saturated sodium bicarbonate and brine. The solution was then dried over magnesium sulfate, filtered and concentrated to give the crude product. Vacuum distillation gave the corresponding acetal (8 g) as a colorless oil: ^{1}H nmr (80 MHz) δ 5.25 (m, 1 H), 3.20 (s, 6 H), 1.74-2.40 (m, 6 H) and 1.65 (br s, 3 H). The crude product was used for the following transformation directly. The acetal obtained from the previous experiment (3.4 g) was heated to 120-135°C in a oil bath, and a mixture of ethyl diazoacetate (6.7 g) and the acetal (3.4 g) was added over a period of 4 h in the presence of copper and bronze powder (1:1 ratio). After being cooled to room temperature, the mixture was filtered.

Vacuum distillation of the filtrate at 115-120/0.1 torr gave the crude product (7 g) which was dissolved in acetone (100 mL) contained a few crystals of *p*-TsOH. The mixture was allowed to stand at room temperature for 24 h and concentrated. Water was added to the residue and the mixture was extracted with ether. The extracts were washed with saturated sodium bicarbonate twice and dried over magnesium sulfate. Fitration and concentration gave the crude product which was purified by chromatography. Elution with ethyl acetate and hexane (15:85) gave keto ester **165a** (5 g) as a yellowish oil: ir ($CHCl_3$ cast) 1721 cm^{-1}; ^{1}H nmr (300 MHz) δ 4.15 (m, 2 H), 2.70 (dd, J = 19, 5 Hz, 1 H), 2.57 (dd, J = 19, 2.5 Hz, 1 H), 2.06-2.38 (m, 4 H), 1.73-1.80 (m, 2 H), 1.33 (s, 3 H) and 1.28 (t, J = 7 Hz, 3 H); hrms M$^+$ 196.1098 (calcd. for $C_{11}H_{16}O_3$: 196.1099). A mixture of keto ester **165a** (5 g) in ethanol (100 mL) in the presence of a catalytic amount of sodium acetate was heated under reflux under argon for 8 h and cooled to room temperature. The ethanol was removed *in vacuo* and the residue was subjected to chromatography. Elution with ethyl acetate and hexane (10:90) gave enone ester **165** (4.3 g, 40% yield overall from anisole) as a light yellow oil: ir ($CHCl_3$ cast) 1732 (C=O, ester) and 1681 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz) δ 6.87 (d, J = 10 Hz, 1 H), 5.90 (d, J = 10 Hz, 1 H), 4.15 (q, J = 7 Hz, 2 H), 2.45-2.52 (m, 4 H), 2.11 (ddd, J = 14, 8.5, 5.5 Hz, 1 H), 1.89 (m, 1 H), 1.28 (s, 3 H) and 1.27 (t, J = 7 Hz, 3 H); hrms M$^+$ 196.1091 (calcd. for $C_{11}H_{16}O_3$: 196.1099).

4-Carbethoxymethyl-6-formyl-4-methyl-2-cyclohexenone (166) and 4-carbethoxymethyl-2-formyl-4-methyl-2,5-cyclohexadienone (163)



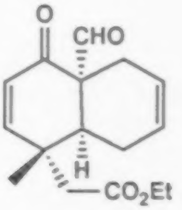
166



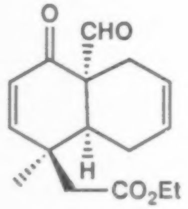
163

Formylation of enone ester **165** (500 mg, 2.55 mol) using the standard conditions (NaH: 210 mg, 5.1 mmol; ethyl formate: 13.6 mL, 168 mmol) gave compound **166** as a yellowish oil: ir ($CHCl_3$ cast) 3400 (br, OH), 1731 (C=O, ester), 1672 and 1651 cm^{-1} (β-hydroxy enone); ^1H nmr (300 MHz) δ 13.76 (br d, J = 5 Hz, 1 H), 7.52 (br d, J = 5 Hz, 1 H), 6.73 (d, J = 10 Hz, 1 H), 6.11 (d, J = 10 Hz, 1 H), 4.13 (q, J = 7 Hz, 2 H), 2.56 (d, J = 15 Hz, 1 H), 2.45 (d, J = 14 Hz, 1 H), 2.38 (d, J = 14 Hz, 1 H), 2.33 (d, J = 15 Hz, 1 H), 1.27 (t, J = 7 Hz, 3 H) and 1.21 (s, 3 H). The crude product was subjected directly to phenylselenenylation-oxidative elimination. Purification by chromatography using ethyl acetate-hexane (40:60) as an eluent gave dienone aldehyde **163** (458 mg, 81% yield) as a colorless oil: ir ($CHCl_3$ cast) 1732 (C=O, ester), 1705 (C=O, aldehyde) and 1666 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 10.20 (s, 1 H), 7.68 (d, J = 3 Hz, 1 H), 6.98 (dd, J = 10, 3 Hz, 1 H), 6.35 (d, J = 10 Hz, 1 H), 4.08 (q, J = 7 Hz, 2 H), 2.71 (d, J = 14 Hz, 1 H), 2.65 (d, J = 14 Hz, 1 H), 1.41 (s, 3 H) and 1.19 (t, J = 7 Hz, 3 H); hrms m/z 207.0657 (M^+-Me, calcd. for $C_{11}H_{11}O_4$: 207.0657) and 135.0447 (base peak, $M^+-CH_2CO_2Et$, calcd. for $C_8H_7O_2$: 135.0446). Anal. calcd. for $C_{12}H_{14}O_4$: C 64.85, H 6.35; found: C 64.99, H 6.09.

(1S*,5R*,6S*)-5-Carbethoxymethyl-1-formyl-5-methylbicyclo[4.4.0]deca-3,8-dien-2-one (168) and (1S*,5S*,6S*)-5-carbethoxymethyl-1-formyl-5-methylbicyclo[4.4.0]deca-3,8-dien-2-one (167)



168

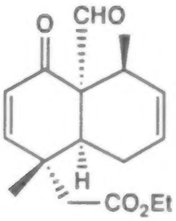


167

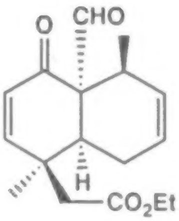
In the same manner as described previously, reaction of dienone ester **163** (42 mg, 0.19 mmol) with 1,3-butadiene (saturated in dichloromethane) using $ZnCl_2$ (78 mg, 0.57 mmol) as a catalyst at room temperature under an argon atmosphere for 3 days followed by the usual work-up gave the crude product. Flash chromatography using ethyl acetate and hexane (20:80) as an eluent gave adducts **168** and **167** (47 mg, 90% yield) as a colorless oil: ir ($CHCl_3$ cast) 1731 (C=O, ester and aldehyde) and 1667 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) two isomers in a ratio of 1.7:1; for the major isomer **168**: δ 9.59 (s, 1 H), 6.95 (d, *J* = 10 Hz, 1 H), 5.94 (d, *J* = 10 Hz, 1 H), 5.73 (br s, 2 H), 4.16 (q, *J* = 7 Hz, 2 H), 2.87 (br d, *J* = 6 Hz, 1 H), 2.02-2.68 (m, 6 H), 1.27 (t, *J* = 7 Hz, 3 H) and 1.16 (s, 3 H); for the minor isomer **167**: δ 9.59 (s, 1 H), 6.96 (d, *J* =

10 Hz, 1 H), 5.96 (d, *J* = 10 Hz, 1 H), 5.73 (br s, 2 H), 4.16 (q, *J* = 7 Hz, 2 H), 2.75 (dd, *J* = 7, 3.5 Hz, 1 H), 2.02-2.68 (m, 6 H), 1.37 (s, 3 H) and 1.17 (t, *J* = 7 Hz, 1 H); hrms M$^+$ 276.1368 (calcd. for $C_{16}H_{20}O_4$: 276.1361).

(1S*,5R*,6S*,10S*)-5-Carbethoxymethyl-1-formyl-5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (169) and (1S*,5S*,6S*,10R*)-5-carbethoxymethyl-1-formyl-5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (170)



169

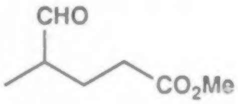


170

Dienone aldehyde **163** (66 mg, 0.30 mmol) was reacted with *trans*-piperylene (0.3 mL, 3.0 mmol) using $ZnCl_2$ (122 mg, 0.90 mmol) as a catalyst at room temperature under an argon atmosphere for 14 h followed by the usual work-up to give the crude product which was subjected to chromatography. Elution with ethyl acetate and hexane (15:85) gave adducts **169** and **170** (78 mg, 90% yield) as a colorless oil: ir ($CHCl_3$ cast) 1729 (C=O, ester and aldehyde) and 1688 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz) two isomers in a ratio of 1.2:1; for the major isomer **169**: δ 9.64 (s, 1 H), 6.65 (d, *J* = 10 Hz, 1 H), 5.99 (d, *J* = 10 Hz, 1 H), 5.55-5.65 (m, 2 H), 4.16 (q, *J* = 7 Hz, 2 H), 2.99 (t, *J* = 6 Hz, 1 H), 2.79 (m, 1 H), 2.43-2.54 (m, 2

H), 2.03-2.27 (m, 2 H), 1.27 (t, J = 7 Hz, 3 H), 1.21 (s, 3 H) and 1.16 (d, J = 7 Hz, 3 H); for the minor isomer **170**: δ 9.62 (s, 1 H), 6.55 (dd, J = 10, 2 Hz, 1 H), 5.94 (d, J = 10 Hz, 1 H), 5.55-5.65 (m, 2 H), 4.17 (q, J = 7 Hz, 2 H), 2.86-2.93 (m, 2 H), 1.39 (s, 3 H), 1.28 (t, J = 10 Hz, 1 H) and 1.23 (d, J = 7 Hz, 3 H); hrms M^+ 290.1518 (calcd. for $C_{17}H_{22}O_4$: 290.1518).

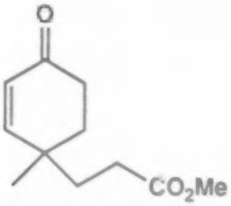
Methyl 4-formylpentanoate (171)



To an ice-cold mixture of pyrrolidine (3 mL, 36 mmol) and potassium carbonate (1.4 g) under an argon atmosphere, was added propanal (1.74 g, 30 mmol) dropwise over a period of 30 min. The mixture was stirred at 0°C for an additional 2 h and filtered. The flask was washed with ether which was then added to the original filtrate and distillation gave enamine (1.8 g, 54% yield). To a solution of the above enamine in acetonitrile (10 mL) at 0°C under argon, was added methyl acrylate (1.8 g, 20 mmol) in acetonitrile (5 mL) dropwise over a period of 10 min. The mixture was stirred at room temperature for 3 h and then heated to reflux for 17 h and cooled to room temperature. Acetic acid (1 mL) in water (9 mL) was added and the mixture was heated to reflux for 3 h and cooled to room temperature again. The acetic acid in the reaction system was neutralized by sodium bicarbonate. Acetonitrile was evaporated *in vacuo* and the remaining mixture was extracted with ether (3 x

10 mL). The extracts were combined, washed with water and brine, and dried over magnesium sulfate. Filtration and concentration gave the crude product which was purified by flash chromatography. Elution with ethyl acetate and hexane (10:90) gave compound **171** (0.58 g, 25% yield, low yield was partially attributed to the volatility of the product) as a colorless oil: ir ($CHCl_3$ cast) 1738 cm^{-1} (C=O, ester and aldehyde); ^1H nmr (300 MHz) δ 9.58 (d, *J* = 2 Hz, 1 H), 3.62 (s, 3 H), 2.40 (m, 1 H), 2.34 (t, *J* = 7 Hz, 2 H), 2.02 (m, 1 H), 1.65 (m, 1 H) and 1.09 (d, *J* = 7 Hz, 3 H); hrms M^+ 142.0631 (calcd. for $C_7H_{10}O_3$: 142.0630).

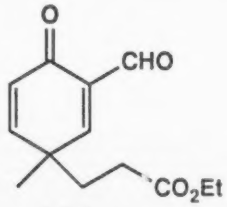
4-(2-Carbomethoxyethyl)-4-methyl-2-cyclohexenone (172)



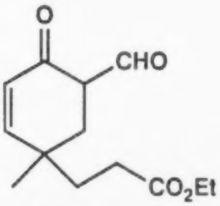
To a mixture of pyrrolidine (1.52 mL, 18 mmol) and potassium carbonate (0.7 g) in THF (5 mL) at 0°C under an argon atmosphere, was added methyl 4-formylpentanoate (**171**) (1.75 g, 12 mmol) in THF (5 mL). The mixture was stirred at 0°C for 2 h and filtered. The flask was washed with THF which was added to the original filtrate. Evaporation of THF and the unreacted pyrrolidine gave enamine (2.43 g) which was dissolved in dry methanol (10 mL) and cooled to 0°C under argon. Methyl vinyl ketone (2 mL, 24 mmol) was added and the solution was stirred at 0°C for 10 h. 2 N HCl (10 mL) was added to the solution and the mixture was stirred at room temperature overnight. Evaporation of methanol *in vacuo* and the remaining aqueous solution was extracted with with dichloromethane (3 x 10 mL). The extracts were combined, washed with 1 N HCl (10 mL) and saturated sodium bicarbonate (10 mL), and dried over magnesium sulfate. Filtration and concentration gave the crude product which was purified by chromatography. Elution with ethyl acetate and hexane (20:80) gave compound **172** (0.60 g, 25% yield) as a colorless oil: ir ($CHCl_3$ cast) 1738 (C=O, ester) and 1682 cm^{-1} (C=O, enone); ^1H nmr (80 MHz) 6.60 (d, *J* = 10 Hz, 1 H), 5.85 (d, *J* = 10 Hz, 1 H), 3.70 (s, 3 H), 1.75-2.55 (m, 4 H) and 1.20 (s, 3 H); hrms M^+ 196.1092 (calcd. for $C_{11}H_{16}O_3$: 196.1099). Anal. calcd. for $C_{11}H_{16}O_3$: C 67.32, H 8.22; found: C 67.10, H 7.97.

4-(2-Carbethoxyethyl)-6-formyl-4-methyl-2-cyclohexenone (173)

4-(2-carbethoxyethyl)-2-formyl-4-methyl-2,5-cyclohexadienone (164)



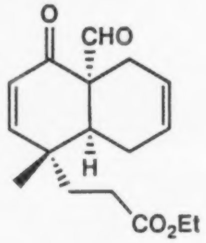
164



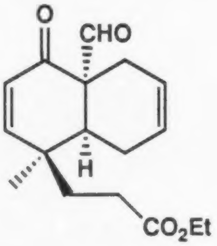
173

Formylation of enone ester **172** (200 mg, 1.02 mmol) gave the keto enol **173** which was subjected to phenylselenenylation-oxidative elimination directly. Flash chromatography of the crude product gave dienone aldehyde **164** (170 mg, 71% yield) as a colorless oil: ir ($CHCl_3$ cast) 1734 (C=O, ester), 1704 (C=O, aldehyde) and 1668 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 10.23 (s, 1 H, -C**H**O), 7.25 (d, *J* = 3 Hz, 1 H), 6.80 (dd, *J* = 10, 3 Hz, 1 H), 6.38 (d, *J* = 10 Hz, 1 H), 4.07 (q, *J* = 7 Hz, 2 H), 2.03-2.16 (m, 2 H), 1.39 (s, 3 H) and 1.22 (t, *J* = 7 Hz, 3 H); hrms M^+ 236.1045 (calcd. for $C_{13}H_{16}O_4$: 236.1048).

(1S*,5R*,6S*)-5-(2-Carbethoxyethyl)-1-formyl-5-methylbicyclo[4.4.0]deca-3,8-dien-2-one (174) and (1S*,5S*,6S*)-5-(2-carbethoxyethyl)-1-formyl-5-methylbicyclo[4.4.0]deca-3,8-dien-2-one (175)



174

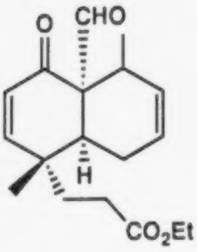


175

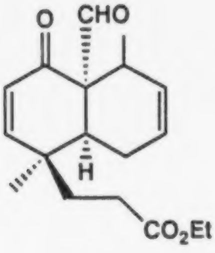
In the same manner as described previously, reaction of dienone aldehyde **164** (46 mg, 0.18 mmol) with 1,3-butadiene (saturated in dichloromethane) using $ZnCl_2$ (80 mg, 0.58 mmol) as catalyst at room temperature under an argon atmosphere for 2.5 days followed by work-up in the usual manner gave the crude product (5:1 mixture of two isomers). Flash chromatogaraphy using ethyl acetate-hexane (15:85) as an eluent gave adduct **174** (6.6 mg, 12% yield) as a colorless oil: ir ($CHCl_3$ cast) 1732 (C=O, ester and aldehyde) and 1667 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz) δ 9.59 (s, 1 H, -C**H**O), 6.63 (d, *J* = 10 Hz, 1 H, -C**H**=CHCO), 5.95 (d, *J* = 10 Hz, 1 H, -CH=C**H**CO), 5.72 (m, 2 H), 4.15 (q, *J* = 7 Hz, 2 H), 2.65-2.74 (m, 2 H), 2.38 (ddd, *J* = 16, 10, 6 Hz, 1 H), 2.32 (m, 1 H), 2.23 (ddd, *J* = 16, 11.7, 5.7 Hz, 1 H), 2.04 (m, 1 H), 1.98 (ddd, *J* = 14, 10, 6 Hz, 1 H), 1.79 (ddd, *J* = 14, 11.7, 5.7 Hz, 1 H), 1.26 (t, *J* = 7 Hz, 3 H) and 1.10 (s, 3 H); ^{13}C nmr (APT) δ 201.30 (a), 198.69 (p), 173.09 (p), 157.34 (a), 127.72 (a), 126.35 (a), 122.67 (a), 60.79 (p), 58.12 (p), 38.79 (p), 36.06 (p), 33.19 (a), 29.79 (p), 27.86 (p), 22.73 (a), 22.47 (p) and 14.24 (a); hrms M$^+$ 290.1513 (calcd. for $C_{17}H_{22}O_4$: 290.1518).

Further elution gave a mixture of adducts **174** and **175** (64% yield) and adduct **175** (2.8 mg, 5% yield) along with recovered **164** (5 mg, 11% yield). For adduct **175**: ^{1}H nmr (300 MHz) δ 9.58 (s, 1 H, -C**H**O), 6.65 (d, *J* = 10 Hz, 1 H), 5.94 (d, *J* = 10 Hz, 1 H), 5.72 (br s, 2 H), 4.20 (q, *J* = 7 Hz, 2 H), 2.65 (dd, *J* = 7, 4.5 Hz, 1 H), 2.30-2.54 (m, 3 H), 2.10 (m, 1 H), 1.80-1.90 (m, 2 H), 1.26 (t, *J* = 7 Hz, 3 H) and 1.23 (s, 3 H).

(1S*,5R*,6S*)-5-(2-Carbethoxyethyl)-1-formyl-5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (176) and (1S*,5S*,6S*)-5-(2-carbethoxyethyl)-1-formyl-5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (177)



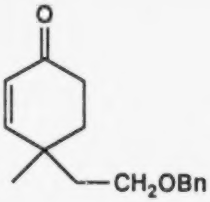
176



177

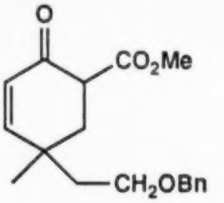
A mixture of dienone aldehyde **164** (79 mg, 0.34 mmol) and *trans*-piperylene (0.35 mL, 3.5 mmol) in benzene was heated to reflux under argon for 42 h and cooled to room temperature. The volatiles were removed *in vacuo* and the residue was subjected to chromatography. Elution with ethyl acetate and hexane (15:85) gave adducts **176** and **177** (25 mg, 25% yield) as a colorless oil: ir ($CHCl_3$ cast) 1732 (C=O, ester and aldehyde) and 1665 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) four isomer in a ratio of 24:11:2.5:1; for the major isomer **176**: δ 9.60 (s, 1H), 6.50 (d, *J* = 10 Hz, 1 H), 6.01 (d, *J* = 10 Hz, 1 H), 5.57-5.65 (m, 2 H), 4.13 (q, *J* = 7 Hz, 2 H), 2.92 (m, 1 H), 2.67 (dd, *J* = 7, 5 Hz, 1 H), 2.28-2.37 (m, 2 H), 1.98-2.10 (m, 12 H), 1.82-1.93 (m, 2 H), 1.27 (t, *J* = 7 Hz, 3 H), 1.13 (s, 3 H) and 1.10 (d, *J* = 7 Hz, 3 H); for the second major isomer **177**: δ 9.84 (s, 1 H), 6.53 (d, *J* = 10 Hz, 1 H), 5.94 (d, *J* = 10 Hz, 1 H), 5.75 (m, 1 H), 5.60 (m, 1 H), 4.12 (q, *J* = 7 Hz, 2 H), 2.99 (t, *J* = 4 Hz, 1 H), 2.60 (dd, *J* = 7, 1 Hz, 1 H) and other peaks are buried underneath the major compounds; hrms M^+ 304.1670 (calcd. for $C_{18}H_{24}O_4$: 304.1674). Further elution gave the recovered starting dienone aldehyde **164** (54 mg, 68% yield).

4-(2-Benzyloxyethyl)-4-methyl-2-cyclohexenone (180)

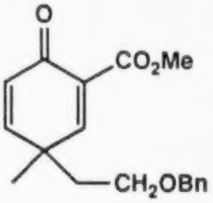


To a solution of diisopropylamine (1.7 mL, 12 mmol) in THF (7 mL) at 0°C under an argon atmosphere, was added *n*-BuLi (6.9 mL, 1.6 M in hexane). The mixture was stirred at 0°C for 15 min and cooled to -78°C. 3-Ethoxy-6-methyl-2-cyclohexenone (1.54 g, 10 mmol) in THF (5 mL) was added dropwise in a period of 15 min. After being stirred at -78°C for 1 h at which time methyl bromoacetate (1.9 mL, 20 mmol) was added in one portion. The mixture was allowed to warm up slowly to room temperature and stirred overnight. Saturated ammonium chloride was added and the mixture was extracted with ether (3 x 20 mL). The extracts were combined, washed with water and brine, and dried over magnesium sulfate. Filtration and concentration gave the crude product. Bulb-to-bulb distillation at 130-140°C/0.6 torr gave the crude alkylation product **179** which was used directly in the following transformation. To a suspension of lithium aluminium hydride (0.8 g) in THF (20 mL) at 0°C under an argon atmosphere, was added dropwise the crude alkylation product **179** (2.10 g) in THF (10 mL). The resulting suspension was stirred for 1 h and then heated under reflux for 1 h. To the mixture cooled to 0°C, were added water (0.12 mL), 3 N NaOH (0.12 mL), water (0.12 mL) and water (0.12 mL) consecutively over a period of 1 h. The resulting grey suspension was stirred for another hour and filtered. The residue was washed thoroughly with ether. The filtrate and washing solution were combined and concentrated to give the crude product (1.9 g). To a suspension of sodium hydride (0.48 g, 11.4 mmol) in THF (10 mL) at 0°C under argon, was added the crude reduction product (1.9 g) in THF (10 mL). The mixture was stirred at 0°C for 1 h and then benzyl bromide (3.25 g, 19 mmol) was introduced. The mixture was stirred at room temperature for 24 h. 1 N HCl was then added to the mixture which was stirred for another 2 h. The mixture was then extracted with ether (3 x 20 mL). The extracts were combined and washed with saturated sodium bicarbonate. After being dried over magnesium sulfate, the solution was filtered and concentrated to give the crude product. Flash chromatography using ethyl acetate and hexane (20:80) gave compound **180** (1.48 g, 66% yield) as a light yellow oil. Alternatively, it could be distilled at 175°C/1 torr to give the pure product as a colorless oil: ir ($CHCl_3$ cast) 1680 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 7.32 (m, 5 H), 6.75 (d, J = 10 Hz, 1 H), 5.86 (d, J = 10 Hz, 1 H), 4.49 (s, 2 H), 3.51-3.64 (m, 2 H), 2.47 (m, 2 H), 2.02 (ddd, J = 15, 7, 7 Hz , 1 H), 1.73-1.90 (m, 3 H); hrms M^+ 244.1459 (calcd. for $C_{16}H_{20}O_2$: 244.1463). Anal. calcd. for $C_{16}H_{20}O_2$: C 78.65, H 8.25; found C 78.93, H 8.52.

4-(2-Benzyloxyethyl)-6-carbomethoxy-4-methyl-2-cyclohexenone (181) and 4-(2-benzyloxyethyl)-2-carbomethoxy-4-methyl-2,5-cyclohexadienone (182)



181



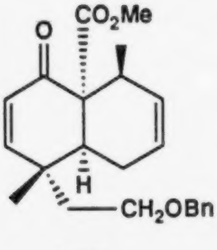
182

To a suspension of sodium hydride (1.05 g, 26.2 mmol) in THF (20 mL) under an argon atmosphere, was added dimethyl carbonate (4.2 mL, 45.5 mmol). The mixture was brought to a boil and then enone **180** (2.78 g, 11.4 mmol) in THF (20 mL) was added dropwise in a period of 30 min. The resulting mixture was heated to reflux for 24 h and cooled to 0°C. Ice-cold 1 N HCl (15 mL) was added cautiously to the mixture and the resulting solution was extracted with ether (3 x 30 mL). The extracts were combined and washed with water and brine. After being dried over magnesium sulfate, the solution was filtered and concentrated to give the crude product. Flash chromatography using ethyl acetate and hexane (10:90) gave keto ester **181** (2.06 g, 60% yield) as a yellowish oil: ir ($CHCl_3$ cast) 1744 (C=O, ester), 1681 (C=O, enone), 1626 and 1592 cm^{-1} (C=C, enol ester); ^{1}H nmr (300 MHz) three isomers in a ratio of 2:1.4:1; isomer 1: δ 7.32 (m, 5 H), 6.81 (dd, *J* = 10, 2 Hz, 1 H), 5.90 (d, *J* = 10 Hz, 1 H), 4.48 (s, 2 H), 3.78 (s, 3 H), 3.50-3.65 (m, 2 H), 1.64-2.50 (m), 1.21 (s, 3 H); isomer 2: δ 6.72 (dd, *J* = 10, 1.5

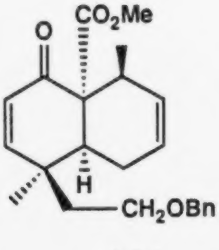
Hz, 1 H), 5.92 (d, *J* = 10 Hz, 1 H), 4.49 (s, 2 H), 3.74 (s, 3 H), 1.18 (s, 3 H); isomer 3: δ 11.87 (s, 1 H), 6.11 (d, *J* = 10 Hz, 1 H), 5.88 (d, *J* = 10 Hz, 1 H), 4.47 (s, 2 H), 3.73 (s, 3 H), 1.07 (s, 3 H); hrms M^+ 302.1515 (calcd. for $C_{18}H_{22}O_4$: 302.1518).

Phenylselenenylation-oxidative elimination of keto ester **181** (0.7 g, 2.32 mmol) followed by flash chromatography using ethyl acetate and hexane (30:70) gave dienone ester **182** (0.59 g, 85% yield) as a light yellow oil: ir (CH_2Cl_2 cast) 1741 (C=O, ester) and 1664 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 7.59 (d, *J* = 3 Hz, 1 H), 7.21-7.36 (m, 5 H), 6.78 (dd, *J* = 10, 3 Hz, 1 H), 6.29 (d, *J* = 10 Hz, 1 H), 4.35 (s, 2 H), 3.80 (s, 3 H), 3.26-3.41 (m, 2 H), 1.97-2.13 (m, 2 H) and 1.32 (s, 3 H); hrms M^+ 300.1353 (calcd. for $C_{18}H_{20}O_4$: 300.1361). Anal. calcd. for $C_{18}H_{20}O_4$: C 71.98, H 6.71; found: C 71.55, H 6.57.

(1R*,5R*,6S*,10S*)-5-(2-Benzyloxyethyl)-1-carbomethoxy-5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (183) and (1R*,5S*,6S*,10S*)-5-(2-benzyloxyethyl)-1-carbomethoxy-5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (184)



183



184

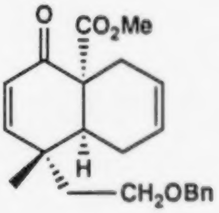
A. using $ZnCl_2$ as catalyst

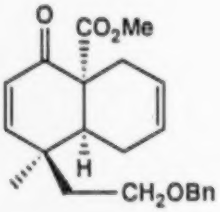
In the same manner as described previously, the reaction of dienone ester **182** (0.75 g, 2.5 mmol) with *trans*-piperylene (2.5 mL, 5 mmol) using $ZnCl_2$ (1.0 g, 7.5 mmol) as a catalyst at 0°C for 36 h followed by the usual work-up gave the crude addition product. Flash chromatography using ethyl acetate and petroleum ether (5:95) gave adduct **183** (0.65 g, 71% yield) as a colorless oil: ir ($CHCl_3$ cast) 1725 (C=O, ester) and 1690 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 7.32 (m, 5 H), 6.29 (dd, J = 10, 2 Hz, 1 H), 5.92 (d, J = 10 Hz, 1 H), 5.57 (ddd, J = 10, 4, 2 Hz, 1 H), 5.50 (ddd, J = 10, 7, 3 Hz, 1 H), 4.52 (d, J = 14 Hz, 1 H), 4.48 (d, J = 14 Hz, 1 H), 3.69 (s, 3 H), 3.58-3.66 (m, 2 H), 2.83 (m, 1 H), 2.75 (ddd, J = 10, 7, 2 Hz, 1 H), 2.16 (dm, J = 18 Hz, 1 H), 1.95 (dm, J = 18 Hz,, 1 H), 1.78 (dd, J = 14, 7 Hz, 1 H), 1.72 (dd, J = 14, 7 Hz, 1 H), 1.22 (d, J = 7 Hz, 3 H) and 1.10 (s, 3 H); ^{13}C nmr (APT) δ 196.33 (p), 174.54 (p), 152.22 (a), 138.37 (p), 130.62 (a), 128.42 (a), 127.57 (a), 127.32 (a), 123.36 (a), 73.13 (p), 66.64 (p), 59.29 (p), 52.37 (a), 43.07 (a), 39.61 (p), 39.10 (p), 37.66 (a), 26.62 (p), 24.22 (a), and 16.87 (a); hrms M^+ 368.1980 (calcd. for $C_{23}H_{28}O_4$: 368.1987).

Further elution gave adduct **184** (0.18 g, 20% yield) as a colorless oil: ir ($CHCl_3$ cast) 1726 (C=O, ester) and 1689 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) δ 7.33 (m, 5 H), 6.29 (dd, J = 10, 2 Hz, 1 H), 5.85 (d, J = 10 Hz, 1 H), 5.56 (ddd, J = 10, 4, 2 Hz, 1 H), 5.47 (ddd, J = 10, 7, 3 Hz, 1 H), 3.71 (s, 3 H), 3.54-3.66 (m, 2 H), 2.75

(m, 1 H), 2.68 (ddd, *J* = 10, 7, 2 Hz, 1 H), 2.30 (dddd, *J* = 19, 7, 4, 3 Hz, 1 H), 2.02 (dm, *J* = 19 Hz, 1 H), 1.93 (ddd, *J* = 14, 8, 6 Hz, 1 H), 1.64 (ddd, *J* = 14, 8, 6 Hz, 1 H), 1.26 (d, *J* = 7 Hz, 3 H) and 1.15 (s, 3 H); ^{13}C nmr (APT) δ 196.23 (p), 174.65 (p), 152.03 (a), 138.16 (p), 130.55 (a), 128.46 (a), 127.71 (a), 127.58 (a), 127.04 (a), 123.37 (a), 73.26 (p), 65.67 (p), 59.22 (p), 52.20 (a), 46.27 (a), 39.81 (p), 38.75 (a), 38.69 (p), 27.04 (p), 24.78 (a) and 16.69 (a); hrms M$^+$ 368.1984 (calcd. for $C_{23}H_{28}O_4$: 368.1987). Continued elution gave the recovered starting enone **182** (70 mg, 9% yield).

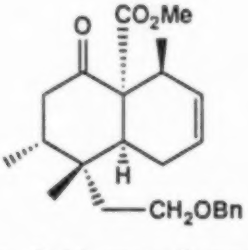
(1R*,5R*,6S*)-5-(2-Benzyloxyethyl)-1-carbomethoxy-5-methylbicyclo[4.4.0]deca-3,8-dien-2-one (185) and (1R*,5S*,6S*)-5-(2-benzyloxyethyl)-1-carbomethoxy-5-methylbicyclo[4.4.0]deca-3,8-dien-2-one (186)





The reaction of dienone ester **182** (97 mg, 0.32 mmol) with 1,3-butadiene (saturated in dichloromethane) using $ZnCl_2$ (140 mg, 1 mmol) as a catalyst at room temperature under an argon atmsophere for 13 h followed by the usual work-up gave the crude adduct which was subjected to chromatography. Elution with ethyl acetate and hexane (20:80) gave adducts **185** and **186** (35.7 mg, 31% yield) as a mixture in a 3:1 ratio: ir ($CHCl_3$ cast) 1742 (C=O, ester 1), 1728 (C=O, ester 2), 1673 cm^{-1} (C=O, enone); ^1H nmr (300 MHz) for the major isomer: δ 7.30 (m, 5 H), 6.69 (d, *J* = 10 Hz, 1 H), 5.94 (d, *J* = 10 Hz, 1 H), 5.66-5.75 (m, 2 H), 4.47 (s, 2 H), 3.70 (s, 3 H), 3.46-3.62 (m, 2 H), 3.00 (t, *J* = 4 Hz, 1 H), 2.74 (dm, *J* = 17 Hz, 1 H), 2.07-2.23 (m, 3 H), 1.96 (dt, *J* = 15, 7 Hz, 1 H), 1.72 (dt, *J* = 15, 7 Hz, 1 H) and 1.09 (s, 3 H); for the minor isomer: δ 7.30 (m, 5 H), 6.71 (d, *J* = 10 Hz, 1 H), 5.93 (d, *J* = 10 Hz, 1 H), 5.66-5.75 (m, 2 H), 4.50 (s, 2 H), 3.70 (s, 3 H), 3.44-3.62 (m, 2 H), 2.75 (m, 1 H), 2.64 (dm, *J* = 18 Hz, 1 H), 2.44 (dm, *J* = 18 Hz, 1 H), 2.07-2.23 (m), 1.85 (t, *J* = 7 Hz, 1 H), 1.84 (t, J = 7 Hz, 1 H) and 1.21 (s, 3 H); hrms M^+ 354.1830 (calcd. for $C_{22}H_{26}O_4$: 354.1831).

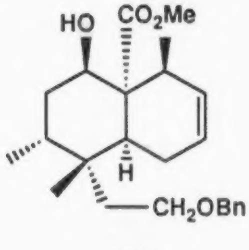
(1R*,4R*,5R*,6S*,10S*)-5-(2-Benzyloxyethyl)-1-carbomethoxy-4,5,10-trimethylbicyclo[4.4.0]dec-8-en-2-one (187)



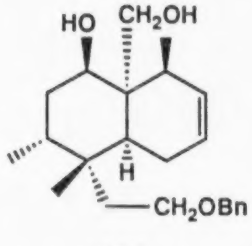
A mixture of CuI (155 mg, 0.82 mmol) and ether (5 mL) in a flame dried round bottom flask under argon was cooled to 0°C. Methyllithium (1.2 mL, 1.4 M in ether) was introduced dropwise (a yellow precipitate formed and then redissolved) and the mixture was stirred at 0°C for 1 h. Compound **183** (96 mg, 0.36 mmol) in ether (2 mL) was added slowly (a yellow precipitate formed) and the mixture was stirred for another hour. Saturated ammonium chloride was added and the mixture was extracted with ether (3 x 10 mL). The extracts were combined, washed with water and brine, and dried over magnesium sulfate. Filtration and concentration gave the crude product which was subjected to chromatography. Elution with ethyl acetate and hexane (10:90) gave compound **187** (98.5 mg, 98% yield) as a colorless oil: ir ($CHCl_3$ cast) 1718 cm^{-1} (br, C=O, ester and ketone); ^1H nmr (300 MHz) δ 7.45 (m, 5 H), 5.57 (ddd, *J* = 10, 3, 2 Hz, 1 H), 5.50 (ddd, *J* = 10, 6, 3 Hz, 1 H), 4.56 (d, *J* = 12 Hz, 1 H), 4.49 (d, *J* = 12 Hz, 1 H), 3.73 (m, 1 H), 3.72 (s, 3 H), 3.57 (m, 1 H), 2.83 (m, 1 H), 2.77 (dd, *J* = 10, 7 Hz, 1 H), 2.52 (m, 1 H), 2.09-2.25 (m, 3 H), 1.95 (m, 1 H), 1.64-1.81 (m, 2 H), 1.12 (d, *J* = 7 Hz, 3 H), 0.95 (s, 3 H) and 0.89 (d, *J* = 6.5 Hz, 3 H); ^{13}C nmr (APT) δ 206.00 (p), 174.83 (p), 138.54 (p), 130.28 (a), 128.41 (a), 127.73 (a), 127.60 (a), 123.01 (a), 73.39 (p), 67.15 (p), 62.49 (p), 52.42 (a), 46.40 (a), 46.32 (p), 40.25 (a), 38.89 (p), 38.44 (a), 32.11 (p), 24.86 (p), 24.27 (a) 16.29 (a) and 15.97 (a); hrms M^+ 384.2307 (calcd. for $C_{24}H_{32}O_4$: 384.2300).

(1R*,2R*,4R*,5R*,6S*,10S*)-5-(2-Benzyloxyethyl)-1-carbomethoxy-2-hydroxy-4,5,10-trimethylbicyclo[4.4.0]dec-8-ene (188) and (1S*,2R*,4R*,5R*,6S*,10S*)-5-(2-benzyloxyethyl)-2-

hydroxy-1-(hydroxymethyl)-4,5,10-trimethylbicyclo[4.4.0]dec-8-ene (189)



188

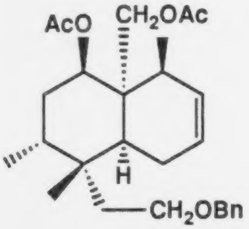


189

To a solution of compound **187** (20 mg, 0.052 mmol) in benzene (5 mL) at room temperature under an argon atmosphere, was added Dibal-H (100 μL, 1 M in toluene). The mixture was stirred for 1.5 h and then ice-cold 6 N HCl was added. The mixture was extracted quickly with ether. The extracts were combined, washed with water and saturated sodium bicarbonate, and dried over magnesium sulfate. Filtration and concentration gave the crude product which was subjected to chromatography. Elution with ethyl acetate and hexane (10:90) gave compound **188** (8 mg, 40% yield) as a colorless oil: ir ($CHCl_3$ cast) 3540 (br, OH) and 1702 cm^{-1} (C=O, ketone); ^{1}H nmr (300 MHz) δ 7.31 (m, 5 H), 5.56 (ddd, *J* = 10, 6, 3 Hz, 1 H), 5.48 (ddd, *J* = 10, 4, 2 Hz, 1 H), 4.48 (s, 2 H), 3.67 (s, 3 H), 3.76 (m, 1 H), 3.60 (ddd, *J* = 11, 9, 4.5 Hz, 1 H), 3.46 (ddd, *J* = 10, 9, 6 Hz, 1 H), 2.66 (m, 1 H), 2.48 (dd, *J* = 10, 8 Hz, 1 H), 2.00-2.15 (m, 2 H), 1.75-1.88 (m, 2 H), 1.55-1.68 (m, 3 H), 1.47 (m, 1 H), 1.13 (d, *J* = 7 Hz, 3 H), 0.85 (s, 3 H) and 0.83 (d, *J* = 6.5 Hz, 3 H); hrms M$^+$ 386.2455 (calcd. for $C_{24}H_{34}O_4$: 386.2457).

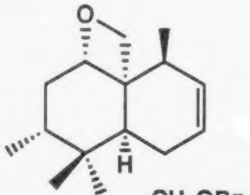
Further elution with ethyl acetate and hexane (40:60) gave diol **189** (8 mg, 43% yield) as a colorless oil: ir ($CHCl_3$ cast) 3424 cm^{-1} (br, OH); ^1H nmr (300 MHz) δ 7.34 (m, 5 H), 5.75 (dm, *J* = 10 Hz, 1 H), 5.64 (dm, *J* = 10 Hz, 1 H), 4.53 (s, 2 H), 4.32 (br d, *J* = 4 Hz, 1 H, -O**H**), 3.85 (dd, *J* = 13, 4 Hz, 1 H), 3.69 (ddd, *J* = 9, 9, 4 Hz, 1 H), 3.59 (m, 1 H), 3.60 (m, 1 H), 3.33 (dd, *J* = 13, 10 Hz, 1 H), 2.83 (m, 1 H), 2.49 (br s, -O**H**), 2.37 (m, 1 H), 2.33 (m, 1 H), 2.21 (m, 1 H), 2.13 (m, 1 H), 2.02 (ddd, *J* = 15, 9, 5 Hz, 1 H), 1.59 (ddd, *J* = 15, 6, 4 Hz, 1 H), 1.53 (dd, *J* = 8, 3 Hz, 2 H), 1.14 (d, *J* = 7 Hz, 3 H), 0.89 (s, 3 H) and 0.82 (d, *J* = 7 Hz, 3 H); ^{13}C nmr (APT) δ 137.18 (p), 133.30 (a), 128.55 (a), 128.22 (a), 128.08 (a), 127.46 (a), 73.52 (p), 70.83 (a), 67.25 (p), 63.88 (p), 44.52 (p), 39.00 (p), 35.58 (p), 35.00 (a), 34.17 (p), 32.92 (a), 30.27 (a), 29.73 (p), 28.13 (p), 26.36 (a), 15.76 (a) and 14.98 (a); hrms m/z 358.2513 (M^+, calcd. for $C_{23}H_{34}O_3$: 358.2508) and 340.2409 (M^+-H_2O, calcd. for $C_{23}H_{32}O_2$: 340.2410); cims $[M+NH_4]^+$ 376.

Diacetate **190**



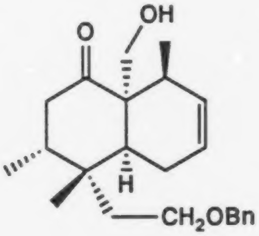
A mixture of diol **189** and acetic anhydride in pyridine in the presence of a trace amount of DMAP was allowed to stand at room temperature in dark for 12 h. The volatiles were removed *in vacuo* and the residue was subjected to chromatography. Elution with ethyl acetate and hexane (10:90) gave diacetate **190** as a colorless oil: ir ($CHCl_3$ cast) 1727 cm^{-1} (C=O, acetate); ^{1}H nmr (300 MHz) δ 7.30 (m, 5 H), 5.62 (dm *J* = 10 Hz, 1 H), 5.38 (dm, *J* = 10 Hz, 1 H), 4.82 (br s, 1 H), 4.49 (s, 2 H), 4.17 (d, *J* = 12 Hz, 1 H), 4.03 (d, *J* = 12 Hz, 1 H), 3.69 (ddd, *J* = 10, 10, 5 Hz, 1 H), 3.55 (ddd, *J* = 10, 10, 6 Hz, 1 H), 2.30 (m, 2 H), 2.10 (m, 2 H), 2.00 (s, 3 H), 1.97 (s, 3 H), 1.55-1.95 (m, 5 H), 1.00 (s, 3 H), 0.96 (br d, *J* = 7 Hz, 3 H), and 0.89 (d, *J* = 7 Hz, 3 H); ^{13}C nmr (APT) δ 170.63 (p), 170.14 (p), 138.57 (p), 130.78 (a), 128.45 (a), 127.56 (a), 127.46 (a), 124.58 (a), 73.13 (p), 71.73 (a), 67.65 (p), 67.07 (p), 42.05 (p), 38.27 (p), 36.33 (a), 34.80 (a), 32.78 (p), 21.51 (a), 20.93 (a) and 15.63 (a); cims $[M+NH_4]^+$ 460.

Compound 191



To a suspension of $LiAlH_4$ (71 mg, 2.1 mmol) in THF (5 mL) at 0°C under an argon atmosphere, was added keto ester **183** (400 mg, 1.04 mmol) in THF (5 mL) dropwise. The mixture was stirred at room temperature overnight and then cooled to 0°C. Water (40 μL), 3 N NaOH (40 μL), water (40 μL) and water (40 μL) was added consecutively in a period of 1 h and the resulting grey suspension was stirred at room temperature for another hour and filtered. The residue was washed thoroughly with ether. The filtrate and the washing solution were combined and concentrated. Chromatography of the crude product using ethyl acetate and hexane (20:80) gave compound **191** (198.5 mg, 39% yield) as a colorless oil: ^{1}H nmr (300 MHz) δ 7.32 (m, 5 H), 5.56 (ddd, *J* = 10, 6, 3 Hz, 1 H), 5.45 (ddd, *J* = 10, 4, 2 Hz, 1 H), 4.53 (s, 2 H), 4.17 (d, *J* = 12 Hz, 1 H), 4.00 (d, *J* = 12 Hz, 1 H), 4.02 (t, *J* = 8 Hz, 1 H), 3.68 (ddd, *J* = 9, 9, 5 Hz, 1 H), 3.56 (ddd, *J* = 9, 5.5, 5.5 Hz, 1 H), 2.74 (m, 1 H), 2.28 (dd, *J* = 10, 7.5 Hz, 1 H), 2.14 (ddd, *J* = 15, 8, 7 Hz, 1 H), 1.96-2.06 (m, 2 H), 1.91 (m, *J* = 8.5, 7 Hz, 1 H), 1.50-1.60 (m, 3 H), 1.22 (d, *J* = 7 Hz, 3 H), 0.85 (s, 3 H) and 0.83 (d, *J* = 7 Hz, 1 H); ^{13}C nmr (APT) δ 137.54 (p), 131.75 (a), 128.48 (a), 128.06 (a), 127.90)a), 123.93 (a), 73.39 (p), 69.65 (a), 66.72 (p), 61.19 (p), 45.42 (p), 39.40 (a), 38.64 (p), 38.50 (p), 35.46 9a), 35.04 (a), 34.29 (p), 26.43 (p), 26.10 (a), 19.35 (a) and 16.02 (a); hrms M$^+$ 340.2393 (calcd. for $C_{23}H_{32}O_2$: 340.2402). Further elution gave diol **189** (165 mg, 33% yield).

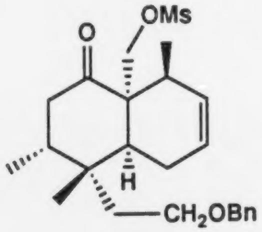
(1S*,4R*,5R*,6S*,10S*)-5-(2-Benzyloxyethyl)-1-(hydroxymethyl)-4,5,10-trimethylbicyclo[4.4.0]dec-8-en-2-one (192)



A mixture of CuI (52 mg, 2.76 mmol) in ether (5 mL) in a flame dried round bottom flask was cooled to 0°C under argon. Methyllithium (7.4 mL, 0.75 M in ether) was added dropwise over a period of 5 min and the solution was stirred at 0°C for 1 h. Enone ester **183** (338 mg, 0.92 mmol) in ether (5 mL) was then introduced slowly over a period of 25 min to the above solution and the yellow mixture was stirred for another hour at which time lithium aluminium hydride (0.16 g, 4.6 mmol) was added to the yellow suspension. The reaction mixture turned into a dark suspension immediately after the addition of lithium aluminium hydride. The dark suspension was stirred for 20 min and ammonium chloride (5 mL) was added carefully until gas evolution ceased followed by the addition of 3 N HCl (15 mL). The mixture was extracted with ether (4 x 20 mL). The extracts were combined, washed with water (2 x 10 mL) and brine, and dried over magnesium sulfate. Filtration and concentration gave the crude product which was subjected to chromatography. Elution with ethyl acetate and hexane (20:80) gave alcohol **192** (203 mg, 62% yield) as a colorless oil: ir (CH_2Cl_2 cast) 3448 (br, OH) and 1692 cm^{-1} (C=O, ketone); ^1H nmr (500 MHz) δ 7.31 (m, 5 H), 5.85 (dt, *J* = 10, 4.5 Hz, 1 H), 5.75 (dd, *J* = 10, 5 Hz, 1 H), 4.49 (s, 2 H), 3.58 (d, *J* = 11 Hz, 1 H), 3.55 (t, *J* = 7 Hz, 1 H), 3.45 (d, *J* = 11 Hz, 1 H), 3.26 (br s, 1 H, O**H**), 2.50 (ddd, *J* = 13,, 6, 6 Hz, 1 H), 2.36 (dd, *J* = 15, 10 Hz, 1 H), 2.00-2.19 (m, 5 H), 1.60 (m, 2 H), 1.10 (d, *J* = 7 Hz, 3 H), 0.97 (s, 3 H) and 0.89 (d, *J* = 6.5 Hz, 3 H); ^{13}C

nmr (APT) δ 219.94 (p), 138.30 (p), 132.20 (a), 128.21 (a), 127.65 (a), 126.60 (a), 73.25 (p), 69.36 (p), 67.01 (p), 55.24 (p), 45.95 (p), 41.63 (a), 37.32 (p), 35.07 (a), 34.84 (p), 33.03 (a), 22.67 (p), 22.53 (a), 17.31 (a) and 15.53 (a); cims $[M+NH_4]^+$ 374. Anal. calcd. for $C_{23}H_{32}O_3$: C 77.49, H 9.05; found: C 76.97, H 9.01.

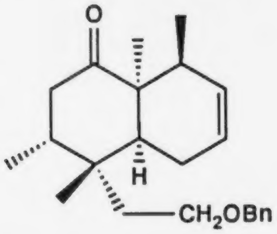
Mesylate 193



To a solution of alcohol **192** (60 mg, 0.17 mmol) and mesyl chloride (65 μL, 0.84 mmol) in THF (5 mL) at 0°C under an argon atmosphere, was added triethylamine (117 μL, 0.84 mmol). The mixture was stirred at 0°C for 1 h and 1 N HCl (5 mL) was added. The mixture was extracted with ether (3 x 10 mL). The extracts were combined, washed with water and brine, and dried over magnesium sulfate. Filtration and concentration gave the crude product which was purified by chromotography. Elution with ethyl acetate and hexane (5:95) gave mesylate **193** (66 mg, 90% yield) as a colorless oil: ir (CH_2Cl_2 cast) 1700 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz) δ 7.35 (m, 5 H), 5.91 (m, 1 H), 5.67 (m, 1 H), 4.54 (d, *J* = 12 Hz, 1 H), 4.51 (d, *J* = 9.5 Hz, 1 H), 4.44 (d, *J* = 12 Hz, 1 H), 4.04 (d, *J* = 9.5 Hz, 1 H), 3.50-3.38 (m, 2 H), 2.96 (s, 3 H), 2.43

(dd, J = 7.5, 4.5 Hz, 1 H), 2.31 (dd, J = 16, 6 Hz, 1 H), 1.96-2.03 (m, 5 H), 1.50-1.72 (m, 2 H), 1.03 (d, J = 7 Hz, 3 H), 1.00 (s, 3 H) and 0.91 (d, J = 6.5 Hz, 3 H); hrms M^+ 434.2127 (calcd. for $C_{24}H_{34}O_5S$: 434.2127).

(1S*,4R*,5R*,6S*,10S*)-5-(2-Benzyloxyethyl)-1,4,5,10-tetramethylbicyclo[4.4.0]dec-8-en-2-one (194)



A mixture of mesylate **193** (50 mg, 0.11 mmol), NaI (173 mg, 1.15 mmol) and zinc metal (151 mg, 2.3 mmol) in DMF (5 mL) was heated to reflux under an argon atmosphere for 7.5 h and cooled to room temperature. The mixture was filtered and the flask was washed with dichloromethane which was added to the original filtrate. The solution was then partitioned between dichloromethane and water. The organic layer was washed with water and dried over magnesium sulfate. Filtration and concentration gave the crude product which was subjected to chromatography. Elution with ethyl acetate and hexane (5:95) gave compound **194** (7.8 mg, 20% yield) along with two unidentified products. For **194**, ir ($CHCl_3$ cast) 1703 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz) δ 7.31 (m, 5 H), 5.85 (m, 1 H), 5.72 (m, 1 H), 4.50 (s, 2 H), 3.50-3.59 (m, 2 H), 2.20 (dd, J = 8, 4 Hz, 1 H), 1.98-2.14

(m, 5 H), 1.94 (t, J = 7 Hz, 1 H), 1.24 (s, 3 H), 0.98 (d, J = 7 Hz, 3 H), 0.96 (s, 3 H) and 0.89 (d, J = 6.5 Hz, 3 H); hrms M^+ 340.2392 (calcd. for $C_{23}H_{32}O_2$: 340.2402).

References and Notes

(1) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98.

(2) Desimoni, G.; Tacconi, G.; Bario, A.; Pollini, G. P. *Natural Product Syntheses through Pericyclic Reactions*; ACS Monograph 180; American Chemicalla Society; Washington, DC, 1984; Chapter 5.

(3) Helmchen, G.; Karge, R.; Weetamn, J. *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer Verlag: New York, 1986; P. 261.

(4) Sauer, J.; Sustmann, R. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 773 and 779.

(5) Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753.

(6) Cohen, N.; Banner, B.; Eichel, W.; Valenta, Z.; Dickenson, R. *Synth. Commun.* **1978**, *8*, 427.

(7) Das, J.; Kubela, R.; MacAlpine, G.; Stojanac, Z.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3308.

(8) Trost, B. M.; Godleski, S. A.; Genet, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930.

(9) Trost, B. M.; Godleski, S. A.; Belletire, J. L. *J. Org. Chem.* **1979**, *44*, 2052.

(10) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.

(11) Woodward, R. B.; Hoffmann, R. *Angew. Chem.* **1969**, *8*, 781.

(12) Houk, K. N.; Lin, Y.-T.; Brown, F. K. *J. Am. Chem. Soc.* **1986**, *108*, 554.

(13) Dewar, M. J. S.; Olivella, S.; Rzepa, H. S. *J. Am. Chem. Soc.* **1978**, *100*, 5650.

(14) Dewar, M. J. S.; Olivella, S.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1986**, *108*, 5771.

(15) Alder, K.; Stein, G. *Angew. Chem.* **1937**, *50*, 510.

(16) Sauer, J. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 16.

(17) Stockmann, H. *J. Org. Chem.* **1961**, *26*, 2025.

(18) Martin, J. G.; Hill, R. K. *Chem. Rev.* **1961**, *61*, 537.

(19) Sauer, J. *Angew. Chem.* **1966**, *78*, 233.

(20) Titov, Y. A. *Russ. Chem. Rev.* **1962**, *31*, 267.

(21) Eisentein, O.; Lefour, J. M.; Anh, N. T.; Hudson, R. F. *Tetrahedron* **1977**, *33*, 523.

(22) Epiotis, N. D. *J. Am. Chem. Soc.* **1973**, *95*, 5624.

(23) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976.

(24) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361.

(25) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092.

(26) Fleming, I.; Gianni, F. L.; Mah, T. *Tetrahedron Lett.* **1976**, 881.

(27) Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436.

(28) Kakushima, M.; Espinosa, J.; Valenta, Z. *Can. J. Chem.* **1976**, *54*, 3304.

(29) Inukai, T.; Kojima, T. *J. Org. Chem.* **1967**, *32*, 869.

(30) Inukai, T.; Kojima, T. *J. Org. Chem.* **1971**, *36*, 924.

(31) Marx, J. N.; Norman, L. R. *J. Org. Chem.* **1975**, *40*, 1602.

(32) Inukai, T.; Kojima, T. *J. Org. Chem.* **1966**, *31*, 1121.

(33) Lutz, E. F.; Bailey, G. M. *J. Am. Chem Soc.* **1964**, *86*, 3899.

(34) Kreiser, W.; Haumesser, W.; Thomas, A. F. *Helv. Chim. Acta.* **1974**, *57*, 164.

(35) Inukai, T.; Kojima, T. *J. Org. Chem.* **1966**, *31*, 2032.

(36) Sauser, J.; Kredel, J. *Tetrahedron Lett.* **1966**, 731.

(37) Williamson, K. L.; Hsu, Y. F. L. *J. Am. Chem. Soc.* **1970**, *92*, 7385.

(38) Stojanac, Z.; Dickenson, R.; Stojanac, N.; Valenta, Z. *Can. J. Chem.* **1975**, *53*, 616.

(39) Tou, J. S.; Reusch, W. *J. Org. Chem.* **1980**, *45*, 5012.

(40) Paquette, L. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Chapter 7.

(41) Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1984**, 876.

(42) Walborsky, H. M.; Barash, L.; Davis, T. C. *Tetrahedron* **1963**, *19*, 2333.

(43) Walborsky, H. M.; Barash, L.; Davis, T. C. *J. Org. Chem.* **1961**, *26*, 4778.

(44) Oppolzer, W.; Chapuis, C.; Dao, G. M.; Reichlin, D.; Godel, T. *Tetrahedron Lett.* **1982**, *23*, 4781.

(45) Oppolzer, W.; Dupuis, D.; Poli, G.; Raynham, T. M.; Bernardinelli, S. *Tetrahedron Lett.* **1988**, *29*, 5885.

(46) Reed, L. A., III.; Davis, J.; Choy, W.; Masamune, S. *J. Org. Chem.* **1983**, *48*, 4441.

(47) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**,

104, 2269.

(48) Oppolzer, W.; Chapuis, C.; Dao, G. M. *Tetrahedron Lett.* **1984**, *25*, 5383.

(49) Furuta, K.; Iwanaga, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 4507.

(50) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

(51) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261.

(52) Helmchen, G.; Schmierer, R. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 205.

(53) Kozikowski, A. P.; Nieduzak, T. R.; Springer, J. P. *Tetrahedron Lett.* **1986**, *27*, 819.

(54) Menezes, R. F.; Zezza, C. A.; Sheu, J.; Smith, M. B. *Tetrahedron Lett.* **1989**, *30*, 3295.

(55) Trost, B. M.; O'Krongly, D.; Belletire, J. *J. Am. Chem. Soc.* **1980**, *102*, 7595.

(56) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1.

(57) Hashimoto, S.-i.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437.

(58) Takemura, H.; Komeshima, N.; Takahashi, I.; Hashimoto, S.-i.; Ikota, N.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1987**, *28*, 5687.

(59) Bednarski, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.*

1983, *24*, 3451.

(60) Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 6254.

(61) Narasaka, K.; Inoue, M.; Yamada, T. *Chem. Lett.* **1986**, 1967.

(62) Narasaka, K.; Inoue, M.; Okada, N. *Chem. Lett.* **1986**, 1109.

(63) Burnell, D. J.; Valenta, Z. *Can. J. Chem.* **1991**, *69*, 179.

(64) Brown, F. K.; Houk, K. N.; Burnell, D. J.; Valenta, Z. *J. Org. Chem.* **1987**, *52*, 3050.

(65) Winstein, S.; Shatavsky, M.; Norton, C.; Woodward, R. B. *J. Am. Chem. Soc.* **1955**, *77*, 4183.

(66) Williamson, K. L.; Hsu, Y. L.; Lacko, R.; Young, C. H. *J. Am. Chem. Soc.* **1969**, *91*, 6129.

(67) Bianchi, G.; De Micheli, C.; Gamba, A.; Gandolfi, R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 137.

(68) Jones, D. W. *J. Chem. Soc., Chem. Commun.* **1980**, 739.

(69) Macaulay, J. B.; Fallis, A. G. *J. Am. Chem. Soc.* **1990**, *112*, 1136.

(70) Franck-Neumann, M.; Sedrati, M. *Tetrahedron Lett.* **1983**, *24*, 1391.

(71) Breslow, R.; Hoffmann, J. M., Jr.; Perchonock, C. *Tetrahedron Lett.* **1973**, 3723.

(72) Ishida, M.; Aoyama, T.; Kato, S. *Chem. Lett.* **1989**, 663.

(73) Fleming, I.; Michael, J. P. *J. Chem. Soc., Chem. Commun.* **1978**, 245.

(74) Burnell, D. J.; Valenta, Z. *J. Chem. Soc., Chem. Commun.*

1985, 1247.

(75) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1991**, *113*, 5089.

(76) Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4054.

(77) Ishida, M.; Beniya, Y.; Inagaki, S.; Kato, S. *J. Am. Chem. Soc.* **1990**, *112*, 8980.

(78) Anh, N. T. *Tetrahedron* **1973**, *29*, 3227.

(79) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

(80) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.

(81) Auksi, H.; Yates, P. *Can. J. Chem.* **1981**, *59*, 2510.

(82) Yates, P.; Gomes, A.; Burnell, D. J.; Cong, D. D.; Sawyer, J. F. *Can. J. Chem.* **1989**, *67*, 37.

(83) Maat, L.; Peters, J. A.; Prazeres, M. A. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 205.

(84) Krow, G. R.; Carey, J. T.; Zacharias, D. E.; Kraus, E. E. *J. Org. Chem.* **1982**, *47*, 1989.

(85) Gillard, J. R.; Burnell, D. J. *J. Chem. Soc., Chem. Commun.* **1989**, 1439.

(86) Kaftory, M.; Peled, M.; Ginsburg, D. *Helv. Chim. Acta* **1979**, *62*, 1326.

(87) Gleiter, R.; Ginsburg, D. *Pure Appl. Chem.* **1979**, *51*, 1301.

(88) Ginsburg, D. *Tetrahedron* **1983**, *39*, 2095.

(89) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 2630.

(90) Fisher, M. J.; Hehre, W. J.; Kahn, S. D.; Overman, L. E. *J. Am.*

Chem. Soc. **1988**, *110*, 4625.

(91) Grabby, S.; Kluge, H.; Hoppe, H.-U. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 664.

(92) McDougal, P. G.; Rico, J. G.; Van Derveer, D. *J. Org. Chem.* **1986**, *51*, 4492.

(93) Reitz, A. B.; Jordan, A. D., Jr.; Maryanoff, B. E. *J. Org. Chem.* **1987**, *52*, 4800.

(94) Tripathy, R.; Franck, R. W.; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257.

(95) Massager, J. C.; Toupet, L. *Acta Crystallogr., Sect. B: Struct. Sci.* **1986**, *B42*, 371.

(96) Kozikowski, A. P.; Nieduzak, T. R.; Konoike, T.; Springer, J. P. *J. Am. Chem. Soc.* **1987**, *109*, 5167.

(97) Kozikowski, A. P.; Jung, S. H.; Springer, J. P. *J. Chem. Soc., Chem. Commun.* **1988**, 167.

(98) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 663.

(99) Alder, K.; Flock, F. H.; Jenssen, P. *Chem. Ber.* **1956**, *89*, 2689.

(100) Sugimoto, T.; Kobuke, Y.; Furukowa, J. *J. Org. Chem.* **1976**, *41*, 1457.

(101) Gugelchuk, M.; Paquette, L. A. *J. Am. Chem. Soc.* **1991**, *113*, 246.

(102) Paquette, L. A.; Shen, C.-C. *J. Am. Chem. Soc.* **1990**, *112*, 1159.

(103) Paquette, L. A.; Green, K. E.; Gleiter, R.; Schäfer, W.; Gallucci, J. *J. Am. Chem. Soc.* **1984**, *106*, 8232.

(104) Paquette, L. A.; Charumilind, P.; Kravetz, T. M.; Böhm, M. C.; Gleiter, R. *J. Am. Chem. Soc.* **1983**, *105*, 3126.

(105) Gleiter, R.; Paquette, L. A. *Acc. Chem. Res.* **1983**, *16*, 328.

(106) Brown, F. K.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 1971.

(107) Kim, M.; Kawada, K.; Gross, R. S.; Watt, D. S. *J. Org. Chem.* **1990**, *55*, 504.

(108) Oppolzer, W.; Petrzilka, M. *J. Am. Chem. Soc.* **1976**, *98*, 6722.

(109) Harayama, T.; Taketami, M.; Inubushi, Y. *Chem. Pharm. Bull. Jpn.* **1979**, *27*, 726.

(110) Grieco, P. A.; Vidari, G.; Ferino, S. *Tetrahedron Lett.* **1980**, 1619.

(111) Liotta, D.; Saindane, M.; Barnum, C. *J. Am. Chem. Soc.* **1981**, *103*, 3224.

(112) Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, 1897.

(113) Fukumoto, K.; Chihiro, M.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2569.

(114) Trost, B. M.; Caldwell, C. G.; Murayama, E.; Heissler, D. *J. Org. Chem.* **1983**, *48*, 3252.

(115) Boger, D. L.; Mullican, M. D.; Helberg, M. R.; Patel, M. *J. Org. Chem.* **1985**, *50*, 1904.

(116) Bartlett, P. D.; Woods, G. F. *J. Am. Chem. Soc.* **1940**, *62*,

2933.

(117) Angell, E. C.; Fringuelli, F.; Pizzo, F.; porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1986**, *51*, 2642.

(118) Angell, E. C.; Fringuelli, F.; Minuti, L.; Pizzo, F.; Taticchi, A.; Wenker, E. *J. Org. Chem.* **1986**, *51*, 5177.

(119) Angell, E. C.; Fringuelli, F.; Minuti, L.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1986**, *51*, 2649.

(120) Angell, E. C.; Fringuelli, F.; Guo, M.; Minuti, L.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1988**, *53*, 4325.

(121) Fringuelli, F.; Guo, M.; Minuti, L.; Pizzo, F.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1989**, *54*, 710.

(122) Liu, H. J.; Browne, E. N. C. *Tetrahedron Lett.* **1977**, 2929.

(123) Liu, H. J.; Browne, E. N. C. *Can. J. Chem.* **1979**, *57*, 377.

(124) Liu, H. J.; Browne, E. N. C. *Can. J. Chem.* **1981**, *59*, 601.

(125) Liu, H. J.; Browne, E. N. C. *Can. J. Chem.* **1987**, *65*, 1262.

(126) Anh, N. T.; Canadell, E.; Eisenstein, O. *Tetrahedron* **1978**, *34*, 2283.

(127) Liu, H. J.; Browne, E. N. C.; Chew, S. Y. *Can. J. Chem.* **1988**, *66*, 2345.

(128) Fringuelli, F.; Taticchi, A.; Wenkert, E. *Organic Preparations and Procedures Int.* **1990**, *22*, 133.

(129) Niwa, M.; Yamamura, S. *Tetrahedron Lett.* **1981**, *22*, 2789.

(130) Seaman, F.; Bohlmann, F.; Zdero, C.; Mabry, T. J. *Diterpenes of Flowering Plants, Compositae (Asteraceae)*; Springer

Verlag: Heidelberg, 1990.

(131) Hanson, J. R. *Natural Product Reports* **1989**, *6*, 347.

(132) Cruse, W. B. T.; James, M. N. T.; Al-Shamma, A. A.; Beal, J. K.; Doskotch, R. W. *J. Chem. Soc., Chem. Commun.* **1971**, 1278.

(133) Anthonsen, T.; Henderson, M. S.; Martin, A.; Murray, R. D. H.; McCrindle, R.; McMaster, D. *Can. J. Chem.* **1973**, *51*, 1332.

(134) Henderson, M. S.; McCrindle, R.; McMaster, D. *Can. J. Chem.* **1973**, *51*, 1346.

(135) Misra, R.; Pandey, R. C.; Dev, S. *Tetrahedron Lett.* **1968**, 2681.

(136) Yamamura, S.; Ito, M.; Niwa, M.; Hasegawa, I.; Ohba, S.; Saito, Y. *Tetrahedron Lett.* **1981**, *22*, 739.

(137) Anthonsen, T.; McCrindle, R. *Acta Chem. Scand.* **1969**, *23*, 1068.

(138) Okazaki, T.; Ohsuka, A.; Kotabe, M. *Nippon Kagaku Kaishi* **1973**, 584.

(139) Nishino, C.; Manabe, S.; Kazui, M.; Matsuzaki, T. *Tetrahedron Lett.* **1984**, *25*, 2809.

(140) Anderson, A. B. R.; McCrindle, R.; Nakamura, E. *J. Chem. Soc., Chem. Commun.* **1974**, 453.

(141) Ferguson, G.; Marsh, W. C.; McCrindle, R.; Nakamura, E. *J. Chem. Soc., Chem. Commun.* **1975**, 299.

(142) McCrindle, R.; Nakamura, E.; Anderson, A. B. *J. Chem. Soc., Perkin Trans. 1* **1976**, *15*, 1590.

(143) Silva, M.; Sammes, P. G. *Phytochem.* **1973**, *12*, 1755.

(144) Chen, T. C.; Guertin, K. R.; Prasad, C. V. C.; Thomas, A. M.; Strunz, G. M.; Salonius, A. *Can. J. Chem.* **1990**, *68*, 1170 and references cited therein.

(145) Tokoroyama, T.; Fujimori, K.; Shimizu, T.; Yamagiwa, Y.; Monden, M.; Iio, H. *J. Chem. Soc., Chem. Commun.* **1983**, 1516.

(146) Iio, H.; Monden, M.; Okada, K.; Tokoroyama, T. *J. Chem. Soc., Chem. Commun.* **1987**, 358.

(147) Tokoroyama, T.; Kanazawa, R.; Yamamoto, S.; Kamikawa, T.; Suenaga, H.; Miyabe, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1720.

(148) Tokoroyama, T.; Matsuo, K.; Kubota, T. *Tetrahedron* **1978**, *34*, 1907.

(149) Tokoroyama, T.; Matsuo, K.; Kotsuki, H.; Kanazawa, R. *Tetrahedron* **1980**, *36*, 3377.

(150) Tokoroyama, T.; Tsukamoto, M.; Asada, T.; Iio, H. *Tetrahesron Lett.* **1987**, *28*, 6645.

(151) Tokoroyama, T.; Tsukamoto, M.; Iio, H. *Tetrahedron Lett.* **1984**, *25*, 5067.

(152) Plieninger, H.; Ege, G.; Fisher, R.; Hoffmann, W. *Chem. Ber.* **1961**, *94*, 2106.

(153) Kazmierczak, F.; Helquist, P. *J. Org. Chem.* **1989**, *54*, 3988.

(154) Gravel, D.; Vaziri, C.; Rahal, S. *J. Chem. Soc., Chem.Commun.* **1972**, 1323.

(155) Liotta, D.; Barnum, C.; Puleo, R.; Zima, G.; Bayer, C.; Kezar, H. S., III *J. Org. Chem.* **1981**, *46*, 2920.

(156) Meyers, A. I.; Comins, D. L.; Ronald, D. M.; Henning, R.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 7104.

(157) Meyers, A. I.; Busacca, C. A. *Tetrahedron Lett.* **1989**, *30*, 6977.

(158) Meyers, A. I.; Busacca, C. A. *Tetrahedron Lett.* **1989**, *30*, 6973.

(159) Kozikowski, A. P.; Sugiyama, K.; Huie, E. *Tetrahedron Lett.* **1981**, *22*, 3381.

(160) Kervin, J. F., Jr.; Danishefsky, S. *Tetrahedron Lett.* **1982**, *23*, 3739.

(161) Chou, S. S. P.; Sun, D. J. *J. Chem. Soc., Chem. Commun.* **1988**, 1176.

(162) Danishefsky, S.; Larson, E. R.; Askin, D. *J. Am. Chem. Soc.* **1982**, *104*, 6457.

(163) Proteau, P. J.; Hopkins, P. B. *J. Org. Chem.* **1985**, *50*, 141.

(164) Sano, T.; Toda, J.; Tsuda, Y. *Chem. Pharm. Bull.* **1983**, *31*, 356.

(165) Satchell, D. P. N.; Satchell, R. S. *Chem. Rev.* **1969**, *69*, 251.

(166) House, H. O. *Modern Synthetic Reactions*; Benjamin, W. A. Inc.: Menlo Park, Ca., 1972; pp 1-34 .

(167) House, H. O. *Modern Synthetic Reactions*; Benjamin, W. A. Inc.: Menlo Park, Ca., 1972; pp 145-205 .

(168) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996.

(169) Ainsworth, C. *Org. Synth.* **1963**, *Coll. Vol. 4*, 536.

(170) *Aldrichimica Acta* **1987**, *20*, 53.

(171) Mander, L. N.; Sethi, P. *Tetrahedron, Lett.* **1983**, *24*, 5425.

(172) Ziegler, F. E.; Stirchak, E. P.; Wester, R. T. *Tetrahedron Lett.* **1986**, *27*, 1229.

(173) Förster, H.; Vögtle, F. *Angew, Chem. Int. Ed. Engl.* **1977**, *16*, 429.

(174) Nonhebel, D. C. *Tetrahedron*, **1968**, *24*, 1869.

(175) Liu, H. J.; Shia, K. H. Unpublished results in this laboratory.

(176) Primeau, J. L.; Anderson, R. C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1983**, *105*, 5874.

(177) Jurczak, J.; Tkacz, M. *Synthesis* **1979**, 42.

(178) Franck, R. W.; John, T. V. *J. Org. Chem.* **1983**, *48*, 3269.

(179) Franck, R. W.; John, T. V.; Olejniczak, K. *J. Am. Chem. Soc.* **1982**, *104*, 1106.

(180) Schmidlin, T.; Burckhardt, P. E.; Waspe-Sarcevic, N.; Tamm, C. *Helv. Chim. Acta* **1983**, *66*, 450.

(181) Horton, D.; Machinami, T.; Takagi, Y. *Carbohydr. Res.* **1983**, *121*, 135.

(182) Grieco, P. A.; Zelle, R. E.; Lis, R.; Finn, J. *J. Am. Chem. Soc.* **1983**, *105*, 1403.

(183) Boger, D. L.; Patel, M.; Takusagawa, F. *J. Org. Chem.* **1985**, *50*, 1911.

(184) Zdero, C.; Jakupovic, J.; Bohlmann, F. *Phytochem.* **1990**, *29*, 1231.

(185) Malakov, P. Y.; Papanov, G. Y.; Mollov, N. M. *Tetrahedron Lett.*

1978, 2025.

(186) Fujita, E.; Uchida, I.; Fujita, T. *J. Chem. Soc., Chem. Commun.* **1973**, 793.

(187) Stipanovic, R. D.; Turner, R. B. *J. Org. Chem.* **1968**, *33*, 3261.

(188) Stork, G.; Brizzlara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

(189) Otani, G.; Yamada, S.-I. *Chem. Pharm. Bull.* **1973**, *21*, 2125.

(190) Stork, G.; Danheiser, R. *J. Org. Chem.* **1973**, *38*, 1775.

(191) Kieczykowski, G. R.; Quesada, M. L.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 782.

(192) Nigooi, T. K. Ph.D Thesis, the University of Alberta, Edmonton, Alberta, Canada, 1984; P. 151.

(193) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.

(194) Kende, A. S.; Fludzinski, P. *Org. Synth.* **1985**, *64*, 68.